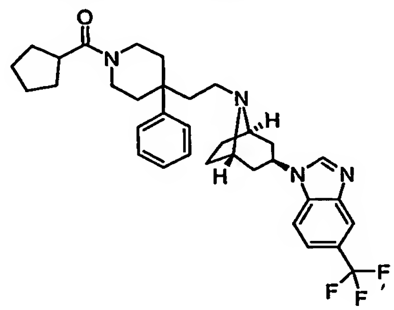
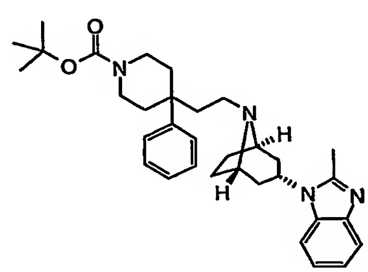
Example 734

exo 1-((1R,5S)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole



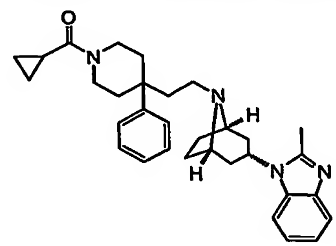
The title compound was prepared from exo 1-{(1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-5-(trifluoromethyl)-1H-benzimidazole (110 mg, 0.228 mmol), which was obtained using analogous chemistry to that described in the synthesis of exo 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as described elsewhere in this application, and cyclopentane carbonyl chloride (48.1 mg, 0.342 mmol). The crude was purified by Plate Purification Method A to afford exo 1-((1*R*,5*S*)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1*H*-benzimidazole as an oil (4.8 mg, 3.6%). ES-LCMS (CLND) *m/z* 579 $(M+H)^+$.

Examples 735-737 were synthesized by deprotecting the Boc-proteced intermediate depicted below and acylation via CDI method, described in example 723.



Example 735

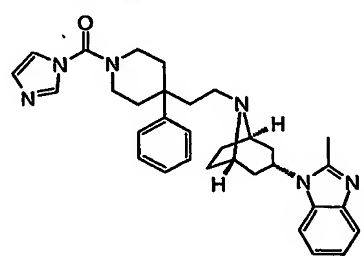
endo 1-((1R,5S)-8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



The title compound was prepared as described in example 723 from cyclopropane carboxylic acid (9.3 mg, 0.108 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2-10% methanol in dichloromethene to afford endo 1-((1R,5S)-8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a colorless oil (41 mg, 77%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.50 (dd, 1H, J=2.8, 2.1 Hz), 7.43-7.35 (m, 4H), 7.25-7.02 (m, 4H), 4.57-4.49 (m, 1H), 3.86-3.76 (m, 2H), 3.38-3.17 (m, 6H), 2.49 (s, 3H), 2.42-2.31 (m, 2H), 2.31-1.77 (m, 10H), 1.65-1.58 (m, 2H), 0.80-0.62 (m, 5H). HRMS *m/z* (M+H) 497.3280 Cal., 497.3274 Obs.

Example 736

endo 1-((1R,5S)-8-{2-[1-(1H-imidazol-1-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

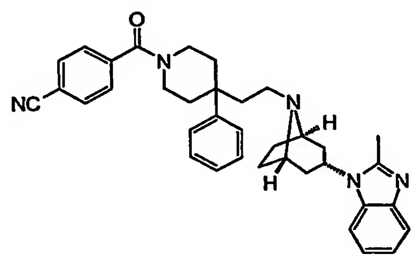


The title compound was prepared as described in example 723 from 2-thiophene carboxylic acid (13.84 mg, 0.108 mmol). The reaction mixture was stirred at room temperature overnight. The crude product was purified by column chromatography on silica gel, eluting with a gradient of 2-10%

methanol in dichloromethene to afford endo 1-((1R,5S)-8-{2-[1-(1H-imidazol-1-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a colorless oil (28.6 mg, 49.4%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.71-7.67 (m, 1H), 7.45-7.39 (m, 2H), 7.33-7.24 (m, 4H), 7.22-7.11 (m, 4H), 4.67-4.62 (m, 1H), 3.91-3.80 (m, 2H), 3.40-3.22 (m, 4H), 2.60 (s, 3H), 2.50-2.34 (m, 4H), 2.10-1.96 (m, 10H), 1.69-1.63 (m, 2H). HRMS *m/z* (M+H) 523.3185 Cal., 523.3190 Obs.

Example 737

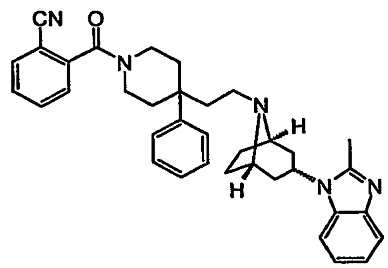
endo 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile



The title compound was prepared as described in example 723 from 4-cyanobenzoic acid acid (47.53 mg, 0.322 mmol). The reaction mixture was stirred at room temperature overnight. The crude was purified by column chromatography on silica gel, eluting with 3% methanol in dichloromethene to afford endo 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile as a colorless oil (58 mg, 32%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 3H), 7.51-7.26 (m, 8H), 7.22-7.13 (m, 2H), 4.65-4.59 (m, 1H), 4.25-4.20 (br m, 1H), 3.55-3.25 (m, 4H), 2.58 (s, 3H), 2.45-2.33 (br m, 3H), 2.21-2.17 (br m, 1H), 1.96-1.80 (m, 11H), 1.76-1.62 (m, 2H). HRMS *m/z* (M+H) 558.3318 Cal., 558.3237 Obs.

Example 738

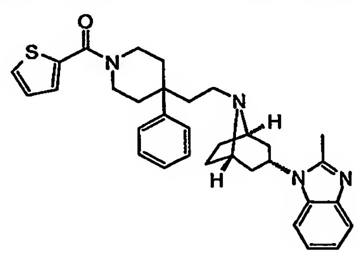
endo 2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile



The title compound was prepared as described in example 710 by coupling 2-carboxybenzonitrile (36.5 mg, 0.247 mmol) *via* HATU (method M) and purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane to afford endo 2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile as a rigid foam (66 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.65 (m, 3H), 7.56-7.15 (m, 10H), 4.69-4.63 (m, 1H), 4.32-4.27 (br m, 1H), 3.45-3.35 (m, 4H), 2.58 (s, 3H), 2.46-2.38 (m, 3H), 2.20-2.19 (br m, 2H), 2.17-1.82 (m, 10H), 1.75-1.62 (m, 2H). HRMS *m/z* (M+H) 558.3233 Cal., 558.3226 Obs.

Example 739

endo 2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

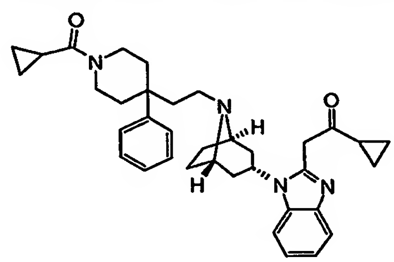


The title compound was prepared from 2-thiophene carboxylic acid (24 mg, 0.186 mmol) using EDCI-HOBT (method P) and purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane to afford endo 2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-

ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole as a colorless oil (14 mg, 14%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68-7.67 (d, 1H, J=6.9 Hz), 7.46-7.15 (m, 10H), 7.13-7.04 (m, 1H), 4.66-4.60 (m, 1H), 4.16-4.00 (br m, 2H), 3.50-3.40 (m, 2H), 3.30-3.25 (br m, 2H), 2.58 (s, 3H), 2.42-2.28 (m, 4H), 2.11-1.98 (m, 10H), 1.72-1.63 (m, 2H). HRMS *m/z* (M+H) 539.2845 Cal., 539.2859 Obs.

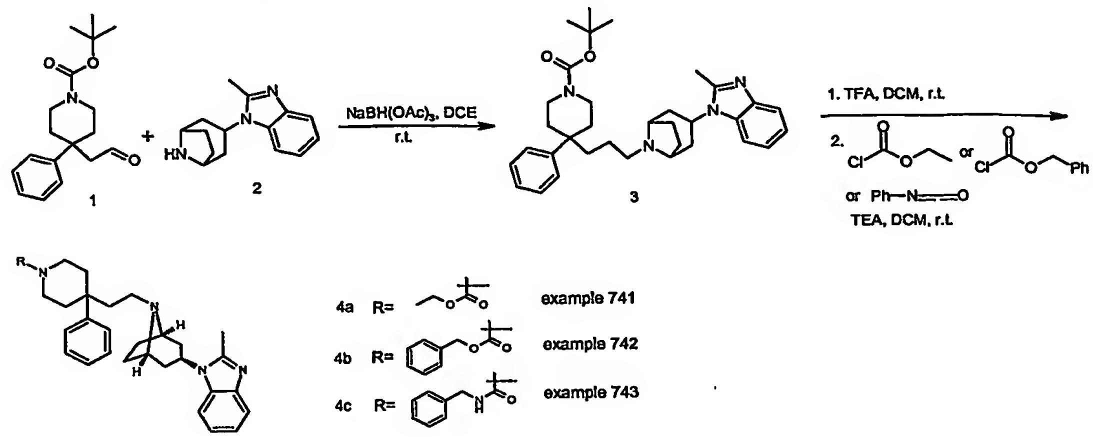
Example 740

endo 1-cyclopropyl-2-[1-(8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidine-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol-2-yl]ethanone



The title compound was prepared as described in Example 3, from cyclopropane carbonyl chloride (12.36 mg, 0.118 mmol), *via* acid chloride Method Q, to afford endo 1-cyclopropyl-2-[1-(8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidine-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol-2-yl]ethanone as an off-white foam (26 mg, 43%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76-7.72 (m, 1H), 7.40-7.34 (m, 5H), 7.33-7.18 (m, 3H), 4.56-4.54 (m, 1H), 4.23-4.19 (m, 2H), 4.15-3.94 (m, 2H), 3.48-3.40 (m, 1H), 3.38-3.26 (m, 3H), 2.42-2.13 (m, 5H), 1.94-1.74 (m, 11H), 1.70-1.62 (m, 2H), 1.13-1.03 (m, 2H), 1.02-0.95 (m, 4H), 0.88-0.75 (m, 2H). HRMS m/z (M+H) 565.3543 Cal., 565.3541 Obs.

Synthesis of carbamates, examples 741-743



Synthesis of 3 of the above scheme:

To a solution of 1 (0.3 g, 1 mmol) in dichloroethane (15 mL), amine 2 (0.032g, 0.148 mmol) was added $NaBH(OAc)_3$ (0.424 g, 2 mmol). The mixture was stirred at r.t. overnight, and then quenched with saturated sodium bicarbonate solution, extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. Purification by chromatotron with 5% MeOH and 0.5% ammonium hydroxide in methylene chloride gave 0.267 g as white solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.62-7.59 (1H, m), 7.36-7.28 (5H, m), 7.20-7.18 (1H, m), 7.14-7.10 (2H, m), 4.43-4.34 (1H, m), 3.68-3.60 (2H, broad), 3.24 (2H, broad s), 3.18 (2H, td, J=9.3 Hz, 2.5 Hz), 2.48 (3H, s), 2.39 (2H, broad t, J=11.9 Hz), 2.20-2.18 (4H, broad), 1.88-1.74 (6H, broad m), 2.10-1.97 (3H, m), 1.79-1.65 (6H, m), 1.55 (2H, d, J=8.1 Hz), 1.47 (2H, dd, J=5.2 Hz, 3.5 Hz), 1.40 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 155.20, 151.20, 144.83, 143.19, 133.75, 128.82, 126.82, 126.37, 121.96, 121.69, 119.42, 111.49, 79.53, 58.71, 48.38, 46.41, 41.38, 40.66, 39.43, 35.75, 34.42, 28.69, 26.88, 14.96. LRMS: calcd. for $C_{34}H_{45}Cl_2N_4O_2$ $(M+H)^+$ 611.3.

Synthesis of 4a-4c of the above scheme:

Deprotection of Boc with 25% TFA in dichloromethane at r.t. was followed by quenching with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried, filtered and

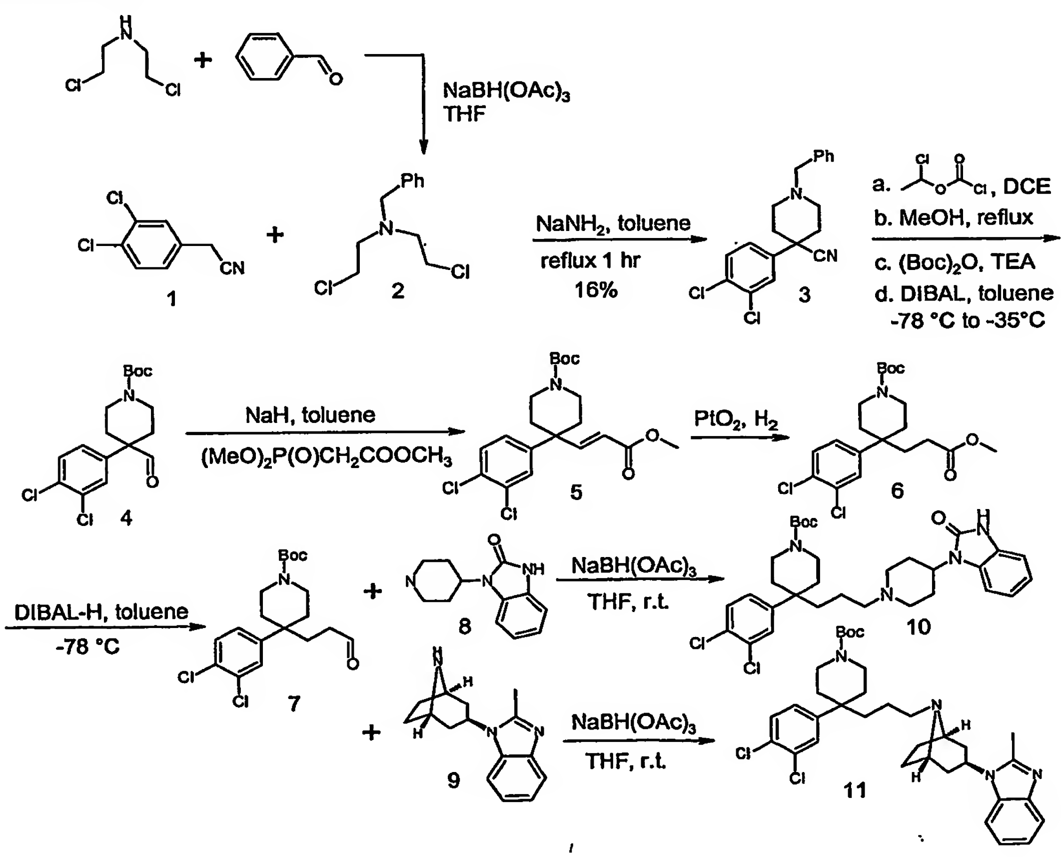
concentrated. 1 eq. of chloroformates or phenyl isocyanate and 3 eq. triethyl amine were used at r.t. until the reactions were complete by LC-MS. The final products were purified by PHPLC.

Example 741: 1.7 mg. HRMS: calcd. for $C_{31}H_{41}N_4O_2$ $(M+H)^+$ 501.3230, found: 501.3205.

Example 742: 1.3 mg. HRMS:calcd. for $C_{36}H_{43}N_4O_2$ $(M+H)^+$ 548.3389, found: 548.3405.

Example 743: 1.0 mg. HRMS: calcd. for $C_{35}H_{42}N_5O$ $(M+H)^+$563.3386, found: 563.3379.

The synthesis of analogues with C3-linker dichloro analogues



Synthesis of 2 of the above scheme:

To a suspension of bis(2-chloroethyl)amine hydrochloride (22.48 g, 125.9 mmol) in dichloroethane (300 mL), benzaldehyde (14.1 mL, 138.5

mmol), triethyl amine (43.8 mL, 314.9 mmol) and $NaBH(OAc)_3$ were added sequentially. The cloudy content was stirred at r.t. overnight. It was then quenched with saturated sodium bicarbonate solution, extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated to give 35.7 g product as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.33-7.31 (5H, m), 3.73 (2H, s), 3.49 (4H, t, J=7.1 Hz), 2.92 (4H, t, J=7.2 Hz). ^{13}CNMR (400 MHz, $CDCl_3$) δ[ppm]: 139.06, 128.83, 128.69, 127.87, 127.62, 127.24, 59.43, 56.59, 42.43.

Synthesis of 3 of the above scheme:

To a solution of 1 (1.18 g, 6.32 mmol) in toluene (50 mL), $NaNH_2$ (1.48 g, 50% in toluene, 18.96 mmol) was added at r.t. (the content turned red upon the addition of sodium amide). The mixture was then heated to reflux for 1 hour. The reaction was quenched with HCl (0.1N, 50 mL). The content pH was adjusted to ~11 with NaOH (50% aqous solution). The organic layer was separated. The aquous layer was extracted twice with ethyl acetate. The combined organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography with hexane/ethyl acetate (8/1 to 4/1) afforded 0.38 g product as red oil (17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.58 (1H, d, J=2 Hz), 7.49 (1H, d, J=14.1 Hz), 7.45-7.28 (6H, m), 3.59 (2H, s), 2.99 (2H, d, J=11.8 Hz), 2.51-2.48 (2H, broad m), 2.07-2.05 (4H, broad). ^{13}CNMR (400 MHz, $CDCl_3$) δ[ppm]: 140.75, 138.18, 133.49, 131.16, 129.29, 128.62, 128.47, 128.15, 127.54, 125.40, 121.47, 63.07, 50.75, 42.62, 36.78. LRMS: calcd. for $C_{19}H_{18}Cl_2N_2$ (M^+) 344.1, found 344.3.

Synthesis of 4 of the above scheme:

To a solution of 3 (3.28 g, 9.53 mmol) in dichloroethane (200 mL), 1-chloroethyl chloroformate (1.54 mL, 14.30 mmol) was added at 0°C and stirred for 15 mins. It was then heated to reflux for 1 hr. After cooling to the r.t., the dichloroethane was removed under reduced pressure. The residue was dissolved in methanol and heated to reflux for 20 mins (reaction was complete by GC-MS). The methanol was removed under reduced pressure. After redissolving the residue in THF (150 mL), $(Boc)_2O$ (3.12 g, 14.3 mmol)

and triethyl amine (4.0 mL, 28.60 mmol) were added. The content was stirred at r.t. overnight. Ethyl acetate was added. The organic layer was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), filtered and concentrated. Flash column chromatography with hexane/EtOAc (8/1 to 6/1) afforded 0.677 g product as yellow solid (20% yield) and another impure fraction (0.894 g, ~85% purity). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.50 (1H, d, J=2.2 Hz), 7.43 (1H, d, J=8.7 Hz), 7.27 (1H, dd, J=8.6 Hz, 2.2 Hz), 4.24 (2H, broad s), 3.12 (2H, broad s), 2.03-1.98 (2H, m), 1.88-1.80 (2H, m), 1.43 (9H, s). ^{13}CNMR (400 MHz, $CDCl_3$) δ[ppm]: 154.45, 140.09, 133.57, 132.87, 131.28, 128.01, 125.31, 120.68, 80.51, 42.72, 41.31, 36.30, 28.59. LRMS: calcd. for $C_{17}H_{20}Cl_2N_2O_2$ (M^+) 354.1 found 354.2.

To a solution of the product from the last step (0.677 g, 1.91 mmol) in toluene (30 mL), DIBAL-H (5.7 mL, 1M in toluene) was added at –78°C. The content was warmed to –35 °C over 3.5 hrs period. The reaction was completed (monitored by GC-MS) and then quenched with saturated ammonium chloride solution (30 mL). The content was extracted with ethyl acetate (GC-MS indicated that incomplete quenching might lead to the cleavage of Boc protecting group. MeOH might be a better choice of quenching reagent). So the content was retreated with $(Boc)_2O$ (2 eq.) and triethyl amine (2 eq.) for 2 hrs. The organic layer was washed with NaOH (0.1N), separated, dried (Na_2SO_4), filtered and concentrated. Flash column chromatography with hexane/ethyl acetate (8/1) afforded 0.14 g (21% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 9.38 (1H, s), 7.40 (1H, d, J=17.4 Hz), 7.36 (1H, d, J=2.2 Hz), 7.10 (1H, J=2.1 Hz), 3.86 (2H, broad s), 3.08 (2H, broad), 2.34 (2H, d, J=13.7 Hz), 1.92 (2H, broad), 1.44 (9H, s). LRMS calcd. for $C_{12}H_{13}Cl_2NO$ $(M\text{-}Boc+H)^+$ 257.0, found 257.1.

<u>Synthesis of 5 of the above scheme</u>:

To a suspension of NaH (0.025 g, 60% in mineral oil, 0.627 mmol) in toluene, trimethyl phosphonoacetate (0.1 mL, 0.627 mmol) was added. The content was stirred at r.t. for 1 hr before 4 (0.14 g, o.392 mmol) in toluene (2 mL) was added (in case of a large scale reaction, an ice bath is necessary to

control the reaction). The content was stirred at r.t. overnight during which it turned cloudy. The reaction was quenched with water. The content was extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4), filtered and concentrated. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: (crude) 7.40 (1H, d, J=8.6 Hz), 7.33 (1H, J=2 Hz), 7.10 (1H, dd, J=8.4 Hz, 2.0 Hz), 6.90 (1H, J=16.1 Hz), 5.67 (1H, J=16.1 Hz), 3.71 (3H, s), 3.52-3.36 (4H, m), 2.08-1.96 (4H, m), 1.44 (9H, s).

Synthesis of 6 of the above scheme:

To a solution of the residue in EtOH (15 mL), PtO_2 was added. The content was stirred under 1 atm H_2 for 3 hrs (the reaction was complete by GC-MS). The content was filtered through celite and concentrated. Flash column chromatography with hexane/ethyl acetate (4/1) afforded 0.123 g (76% yield) product as oil. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.42 (1H, d, J=8.4 Hz), 7.32 (1H, J=2.1 Hz), 7.10 (1H, dd, J=8.6 Hz, 2.2 Hz), 3.64 (2H, broad), 3.57 (3H, s), 3.11 (2H, t, J=10 Hz), 2.07-1.89 (6H, m), 1.72-1.67 (2H, m), 1.43 (9H, s).

Synthesis of 7 of the above scheme:

DIBAL-H (0.593 mL, 1M in toluene, 0.593 mmol) was cooled to –78°C and added into a solution of 6 (0.123 g, 0.296 mmol) in toluene (15 mL) (also cooled to -78°C with a dry ice-acetone bath, necessary to prevent overreduction) dropwise (to keep the internal temperature as low as possible). The content was stirred at -78°C for 2.5 hrs and the reaction was quenched with a cooled MeOH (-78°C) dropwise (the addition needs to be slow to keep the internal temperature low and prevent overreduction). After the addition completed, the content was warmed to r.t. and filtered through celite. The filtrate was washed with brine. The aquous layer was extracted with ethyl acetate. The combined organic layer was dried with Na_2SO_4, filtered and concentrated. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 9.59 (1H, s), 7.41 (1H, d, J=8.4 Hz), 7.37 (1H, d, J=3.8 Hz), 7.31 (1H, dd, J=8.3 Hz, 2.2 Hz), 3.66-3.63 (2H, m), 3.12-3.06 (2H, m), 2.13-2.02 (4H, m), 1.89-1.85 (2H, m), 1.77-1.64 (2H, m), 1.44 (9H, s).

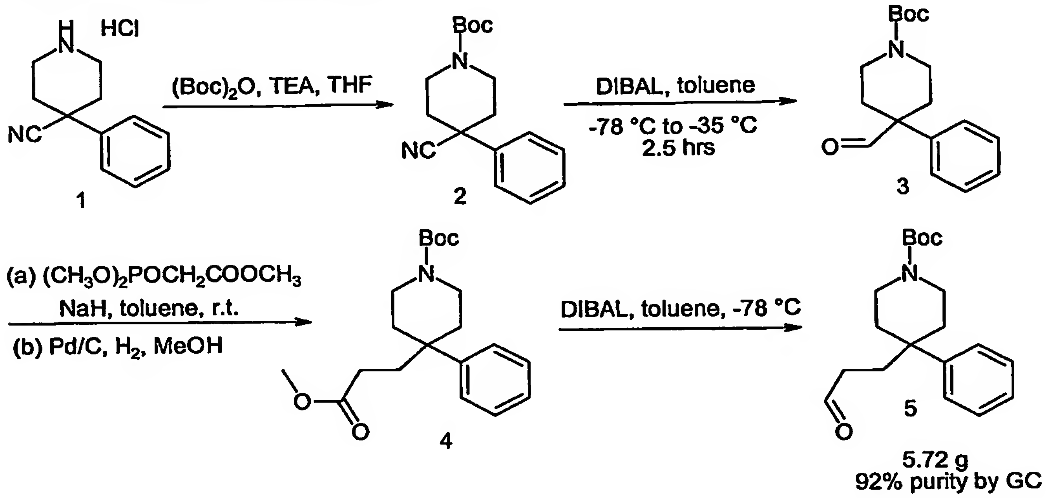
Synthesis of 10 of the above scheme:

To a solution of 7 (1/2 the residue from the last step, ~0.148 mmol) in THF (15 mL), amine 8 (0.032g, 0.148 mmol) was added. The content was stirred at r.t. for 10 mins before $NaBH(OAc)_3$ (0.094 g, 0.444 mmol) was added. It was stirred at r.t. overnight, and then quenched with saturated sodium bicarbonate solution, extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. Prep. TLC purification with 5% MeOH and 0.5% ammonium hydroxide in methylene chloride gave 9 mg product. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 9.13 (1H, s), 7.40 (1H, d, J=8.5 Hz), 7.34 (1H, d, J=1.9 Hz), 7.07 (1H, dd, J=8.4 Hz, 1.9 Hz), 4.32 (1H, broad s), 3.63 (2H, m), 3.12 (2H, broad t, J=10.2 Hz), 2.92 (2H, broad s), 2.42 (1H, broad s), 2.22 (2H, broad s), 2.10-1.97 (3H, m), 1.79-1.65 (6H, m), 1.58 (2H, broad s), 1.43 (9H, s), 1.12-1.08 (2H, broad). HRMS: calcd. for $C_{31}H_{41}Cl_2N_4O_3$ $(M+H)^+$ 587.2556, found 587.2565.

Synthesis of 11 of the above scheme:

Following the route described towards 10, 43 mg of product 11 was synthesized. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.66-7.63 (1H, m), 7.56 (1H, broad s), 7.40-7.36 (2H, m), 7.20-7.13 (3H, m), 4.52-4.43 (1H, m), 3.63 (2H, m), 3.26 (2H, broad s), 3.18 (2H, td, J=9.2 Hz, 2.8 Hz), 2.58-2.48 (5H, broad), 2.33-2.28 (2H, m), 2.07-2.00 (4H, m), 1.76-1.60 (8H, m), 1.44 (9H, s), 1.19 (2H, broad s). LRMS: calcd. for $C_{34}H_{45}Cl_2N_4O_2$ $(M+H)^+$ 611.3, found 611.0.

The synthesis of analogues with C3-linker- unsubstituted scaffold



Synthesis of 2 of the above scheme:

To a suspension of 1 (22 g, 98.8 mmol) in THF (300 mL), TEA (45 mL, 326 mmol) and $(Boc)_2O$ (24 g, 110 mmol) were added and the content was stirred at r.t. overnight, followed by addition of HCl (250 mL, 0.1 N) and the mixture was extracted with ethyl acetate. The organic layer was combined, dried over Na_2SO_4, filtered and concentrated to give 26.2 g product as white crystalline solid (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.46-7.25 (5H, m), 4.26 (2H, brs), 3.18 (2H, brs), 2.07 (2H, d, J=13.5Hz), 1.93 (3H, t, J=9.4Hz), 1.47 (9H, s). ^{13}CNMR (400 MHz, $CDCl_3$) δ[ppm]: 154.67, 139.88, 129.54, 129.38, 128.57, 125.77, 121.60, 80.39, 43.20, 41.52, 36.48, 28.65. LRMS: m/z calcd. for $C_{17}H_{22}N_2O_2$ (M^+) 286.17, found 286.2.

Synthesis of 3 of the above scheme:

DIBAL-H (60 mL, 1M in hexane, 60 mmol) was added to a solution of 2 (8.0 g, 28.0 mmol) in toluene (200 mL) at -78°C with a dry-ice acetone bath. The content was warmed to -35°C over about 2 hrs and stirred at -35°C for another hour. The reaction was quenched with saturated ammonium chloride (100 mL), filtered through celite. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to afford 6.95 g product as light yellow oil (86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 9.40 (1H, s), 7.45-7.25 (5H, m), 3.85 (2H, brs), 3.10 (2H, br), 2.36 (2H, d, J=13.6 Hz), 1.98 (2H, br), 1.44

(9H, s). ^{13}CNMR (400 MHz, $CDCl_3$) δ[ppm]: 201.18, 154.96, 138.34, 129.40, 128.02, 127.16, 79.93, 53.26, 40.88, 30.77, 28.64. LRMS: m/z calcd. for $C_{17}H_{23}NO_3$ 289.2, found 289.2 (M^+).

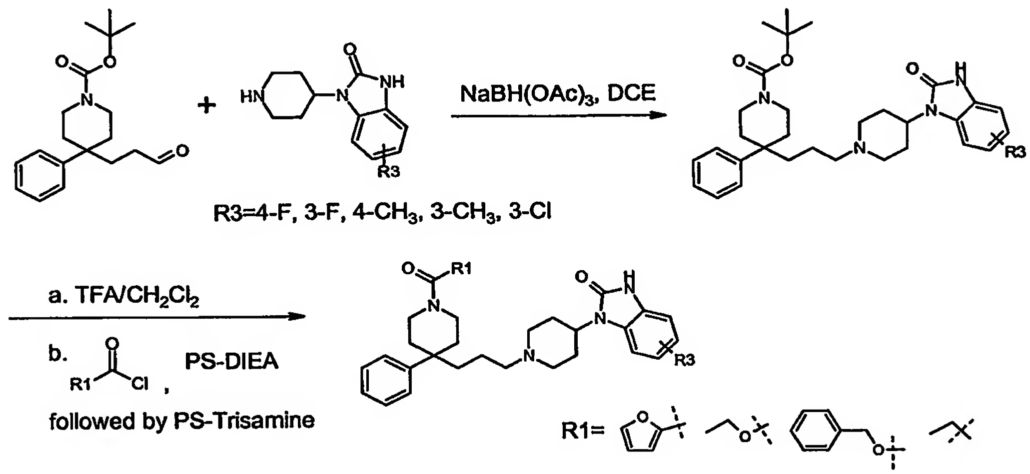
Synthesis of 4 of the above scheme:

To a suspension of NaH (1.15 g, 60% in mineral oil, 28.86 mmol) in toluene (100 mL) at 0°C, trimethyl phosphonoacetate (4.28 mL, 26.45 mmol) was added dropwise and the content was warmed up to r.t. and stirred for 50 mins. A solution of 3 (6.95 g, 24.05 mmol) in toluene (50 mL) was next added and the mixture stirred at r.t. overnight. Following addition of water, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to give 8.26 g product as colorless oil (>90% purity by GC-MS analysis). LRMS: m/z calcd. for $C_{20}H_{27}NO_4$ 345.19, found 345.3 (M^+). The oil from the last step was dissolved in MeOH (200 mL). Pd/C (1g, 5%) was added. The content was stirred under 1 atm H_2 for 2.5 hrs and then filtered through celite. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography with hexane/ethyl acetate (2/1) to give 6.5 g product as colorless oil (78% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.47-7.18 (5H, m), 3.70-3.64 (2H, m), 3.54 (3H, s), 3.12 (2H, m), 2.16-2.12 (2H, m), 1.98-1.87 (4H, m), 1.71-1.64 (2H, m), 1.43 (9H, s). LRMS: m/z calcd. for $C_{20}H_{29}NO_4$ 347.2, found 347.3 (M^+).

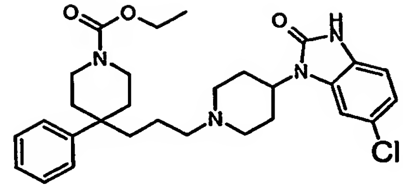
Synthesis of 5 of the above scheme:

DIBAL-H (38 mL, 1M in toluene, 38 mmol) was cooled to –78°C and added into a solution of 4 (6.5 g, 18.73 mmol) in toluene (80 mL) (also cooled to -78°C with a dry ice-acetone bath to prevent overreduction) dropwise (to keep the internal temperature as low as possible). The content was stirred at -78°C for 2.5 hrs and the reaction was quenched with a cooled MeOH (-78°C) dropwise (the addition needs to be slow to keep the internal temperature low and prevent overreduction). After the addition completed, the content was warmed to r.t. and filtered through celite. The filtrate was washed with brine. The aquous layer was extracted with ethyl acetate. The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give 5.72 g prodcut

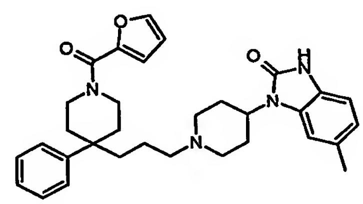
as light green oil (92% purity by GC-MS analysis). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 9.53 (1H, s), 7.46-7.25 (5H, m), 3.73-3.67 (2H, m), 3.10-3.05 (2H, m), 2.17-2.09 (4H, m), 1.90-1.86 (2H, t, J=8.0 Hz), 1.71-1.64 (2H, m), 1.43 (9H, s). LRMS: m/z calcd. for $C_{19}H_{27}NO_3$ 317.2, found 317.3 (M^+).



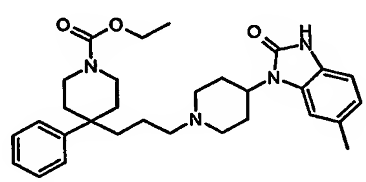
FlexChem Robins Block (24 glass tubes setting) was used for this parallel synthesis. To each glass tube, N_2 was flushed to remove air. Then amines (0.92 eq.), $NaBH(OAc)_3$ (2 eq.), DCE (1 mL), and aldehyde (1 eq) in THF (1 mL) were added sequentially. The block was sealed and rotated at r.t. overnight. The content was drained through a 24 wells filter plate overnight and the filtrate was collect in the same 24 tubes setting. TFA (1 mL) was added to each tube. The block was sealed and shaken for 80 min. The reaction was complete as evident by LC-MS. The gasket was removed and the solvent and TFA were removed under reduced pressure. Saturated sodium bicarbonate was added to each tube followed by DCM. The organic layer was pipeted out to another 24 tubes block. Acid chlorides or chloroformates (2.7 eq) and PS-DIEA (2.7 eq) were added. The block was sealed and rotated overnight. It was cooled in a freezer for 20 mins before the gasket was removed. PS-Trisamine (2.7 eq) was added and the block was sealed and rotated at r.t. for 4 hrs. The content was filtered, concentrated and the residue was purified with Preparative HPLC. All the compounds were obtained as formic acid salt.



Example 744: 2.7 mg product. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 11.00 (1H, s), 7.82 (1H, s), 7.41-7.34 (5H, m), 7.24-7.20 (2H, m), 6.98-6.93 (3H, m), 6.61-6.59 (1H, m), 4.10-4.02 (1H, m), 3.93-3.88 (2H, m), 2.79 (2H, broad d, J=15.4 Hz), 2.26-2.16 (9H, m), 1.92 (2H, broad t, J=11.5 Hz), 1.76 (2H, broad t, J=10.1 Hz), 10.64-10.55 (4H, m), 1.08-1.02 (2H, broad). HRMS: $C_{29}H_{37}ClN_4O_3$ calcd. for $(M+H)^+$ 547.2476, found 547.2480.

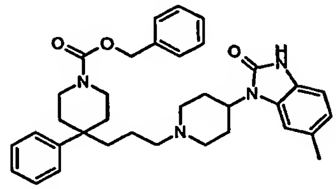


Example 745: 6.7 mg product. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 10.67 (1H, s), 7.79 (1H, s), 7.39-7.33 (5H, m), 7.21-7.18 (1H, t, J=6.7 Hz), 6.97-6.92 (2H, m), 6.78 (2H, dd, J=29.1 Hz, 7.9 Hz), 6.59-6.58 (1H, m), 4.06-4.00 (1H, m), 3.90-3.87 (2H, m), 2.79 (2H, broad d, J=10.5 Hz), 2.28 (3H, s), 2.25-2.15 (6H, m), 1.90 (2H, broad t, J=11 Hz), 1.68-1.63 (2H, m), 1.57-1.48 (4H, m), 1.02 (2H, broad s). HRMS: $C_{32}H_{38}N_4O_3$ calcd. for $(M+H)^+$ 527.3022, found 527.3013.

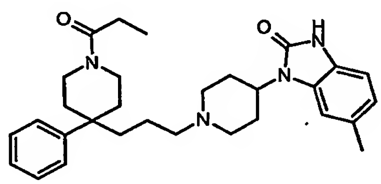


Example 746: 9.6 mg product. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 10.67 (1H, s), 7.34-7.32 (5H, m), 7.19-7.17 (1H, m), 6.96 (1H, s), 6.77 (2H, dd, J=28.8 Hz, 7.7 Hz), 4.02-3.96 (3H, m), 3.06 (2H, m), 2.77 (2H, broad d, J=10.7 Hz), 2.28 (3H, s), 2.24-2.04 (6H, m), 1.88 (2H, broad d, J=11.2 Hz),

1.68-1.63 (2H, m), 1.57-1.51 (4H, m), 1.14 (3H, t, J=7.1 Hz), 1.04 (2H, m). HRMS: $C_{30}H_{40}N_4O_3$ calcd. for $(M+H)^+$ 505.3179, found 505.3152.

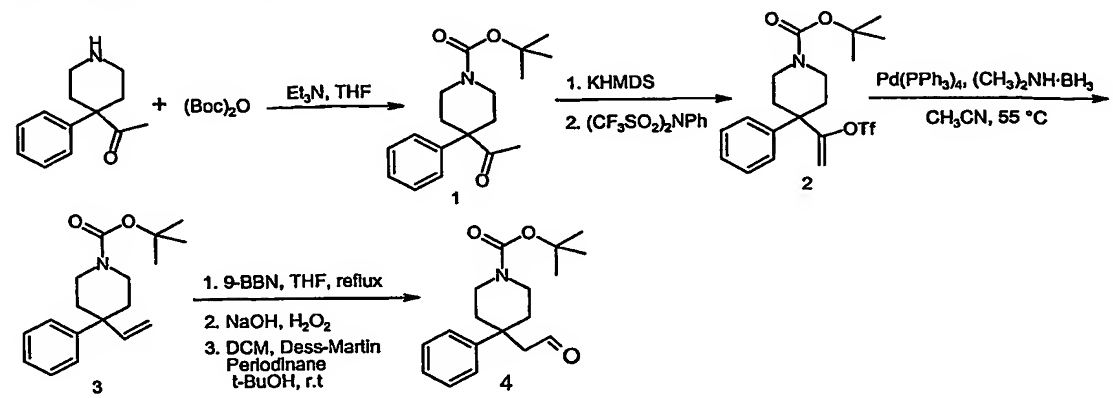


Example 747: 5.3 mg product. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 10.68 (1H, s), 7.39-7.30 (10H, m), 7.23-7.19 (1H, m), 6.98 (1H, s), 6.79 (2H, dd, J=22.4 Hz, 8.9 Hz), 5.06 (2H, s), 4.09-4.01 (1H, m), 3.61 (2H, m), 3.12 (2H, broad s), 2.79 (2H, broad d, J=11.8 Hz), 2.31 (3H, s), 2.28-2.09 (6H, m), 1.91 (2H, t, J=11.3 Hz), 1.70 (2H, t, J=9.9 Hz), 1.60-1.50 (4H, m), 1.07-1.02 (2H, m). HRMS: $C_{35}H_{42}N_4O_3$ calcd. for $(M+H)^+$ 567.3335, found 567.3334.



Example 748: 6.9 mg product. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 10.67 (1H, s), 7.36-7.31 (5H, m), 6.97 (1H, s), 6.78 (2H, dd, J=28.2 Hz, 7.7 Hz), 4.03-4.00 (1H, broad s), 3.78-3.74 (1H, broad), 3.57-3.53 (1H, broad), 3.15-3.10 (1H, m), 3.04-2.99 (1H, m), 2.76 (1H, m), 2.29 (3H, s), 2.27-2.04 (9H, m), 1.85 (1H, broad s), 1.72-1.54 (6H, m), 1.08 (2H, broad s), 0.94 (3H, t, J=7.5 Hz). HRMS: $C_{30}H_{40}N_4O_3$ calcd. for $(M+H)^+$ 489.3229, found 489.3212.

Synthesis of C2-scaffold, BBN method



Synthesis of 1 of the BBN method:

^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.37-7.34 (2H, m), 7.28-7.25 (3H, m), 3.77-3.73 (2H, m), 3.19-3.13 (2H, m), 2.37-2.33 (2H, m), 1.99-1.93 (2H, m), 1.90 (3H, s), 1.43 (9H, s).

Synthesis of 2 of the BBN method:

To a solution of 1 (2.926 g, 9.66 mmol) in toluene (40 mL) at –78 °C, KHMDS (0.5 M in toluene, 21.2 mL) was added dropwise. The content was stirred at –78 °C for 10 mins and the dry ice-acetone bath was removed. The stirring was continued for another 15 mins and the content was cooled back to –78 °C. $(CF_3SO_2)_2NPh$ (4.14 g, 11.6 mmol) in toluene (30 mL) was added. The resulting light brown content was stirred overnight during which it was warmed to r.t. After work-up with water and ethyl acetate, the residue was purified by flash column chromatography with hexane/EtOAc (20/1 to 10/1) to give 3.20 g product (yield 76%). ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.46-7.44 (2H, m), 7.40-7.36 (2H, m), 7.30-7.26 (1H, m), 5.41 (1H, d, J=5.0 Hz), 5.32 (1H, d, J=4.8 Hz), 3.62-3.56 (2H, m), 3.34 (2H, broad s), 2.30-2.24 (2H, m), 2.14-2.08 (2H, m), 1.43 (9H, s). ^{13}C NMR (400 MHz, d_6-acetone) δ[ppm]: 205.32, 160.71, 154.36, 140.30, 128.95, 127.60, 127.41, 103.26, 46.17, 40.65, 39.69, 33.04, 27.94.

Synthesis of 3 of the BBN method:

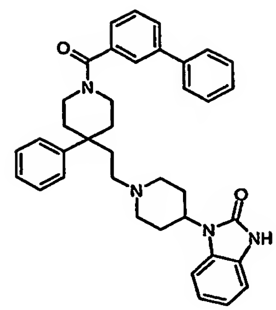
A suspension of K_2CO_3 (0.105 g, 0.76 mmol) and $(CH_3)_2NH{\cdot}BH_3$ (0.04 g, 0.76 mmol) in CH_3CN (1 mL) in a pressure tube was stirred at r.t. for 10

min. A solution of 2 (0.33 g, 0.76 mmol) in CH_3CN (4 mL) was added under nitrogen atomosphere, followed with $Pd(PPh_3)_4$. The tube was sealed. The content was stirred at 65 °C overnight. After cooling to r.t., the content was filtered and concentrated. The residue was purified by flsh column chromatography with hexane/EtOAc (20/1) to give 0.14 g product (64% yield). ^1H NMR (400 MHz, d_6-acetone) δ[ppm]: 7.36-7.29 (4H, m), 7.20-7.16 (1H, m), 5.85 (1H, dd, J=10.8 Hz, 17.7 Hz), 5.11 (1H, d, J=10.9 Hz), 4.95 (1H, d, J=17.6 Hz), 3.50-3.44 (2H, m), 3.41-3.33 (2H, m), 2.07-2.01 (2H, m), 1.96-1.91 (2H, m), 1.43 (9H, s). ^{13}CNMR (400 MHz, d_6-acetone) δ[ppm]: 205.39, 154.55, 145.93, 145.84, 128.67, 126.88, 114.46, 113.49, 78.67, 43.48, 40.70, 34.98, 28.05. Elemental Analysis: calcd. for $C_{18}H_{15}NO_2$ C: 75.22%, H: 8.77%, N: 4.87%, found C 75.16%, H 8.81%, N 4.87%. IR is also available.

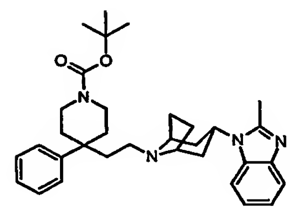
Synthesis of 4 of of the BBN method:

To a solution of 3 (0.267 g, 0.93 mmol) in THF (20 mL) at r.t., 9-BBN (2.8 mL, 0.5 M in THF) was added. The content was heated to reflux overnight. The content was cooled to rt. Sodium hydroxide (0.5 mL, 6.0 M in H_2O) was added, followed with hydrogen peroxide (30% in H_2O, 1 mL). The mixture was stirred at r.t. for 4 hrs, diluted with EtOAc, wsahed with brine. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified with chromatotron (1/1 hexane/EtOAc) to give 0.28 g (99% yield) alcohol. ^1H NMR (400 MHz, d_6-acetone) δ[ppm]: 7.29-7.21 (4H, m), 7.16-7.13 (1H, m), 3.61-3.55 (2H, m), 3.26 (2H, t, J=7.3 Hz), 3.08-3.02 (2H, m), 2.10-2.07 (3H, m), 1.78 (2H, t, J=7.4 Hz), 1.71-1.64 (2H, m), 1.37 (9H, s).

To a suspension of Dess-Matin periodinane in dichloromethane (15 mL) at r.t., t-BuOH was added and the content was stirred for 10 mins. A solution of the alcohol in dichloromethane was added dropwise at r.t. and stirred for 15 mins. The content was diluted with Et2O, washed with 1.3 N NaOH, dried over Na2SO4, filtered, and concentrated. The residue was purified by flash column chromatography with hexane/EtOAc (3/1) to give 0.2 g product as oil (72% yield).

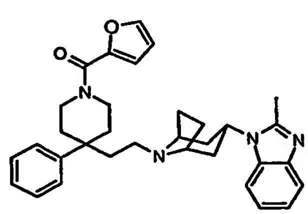


Example 749: HRMS calc. for $C_{38}H_{41}N_4O_2$ $(M+H)^+$ 585.3230, found 585.3201.



Example 750: HRMS calc. for $C_{32}H_{37}N_4O_2$ $(M+H)^+$ 509.2917, found 509.2948. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.92 (1H, s), 7.85 (1H, broad s), 7.71-7.23 (6 H, m), 4.57-4.42 (1H, m), 3.71-3.63 (4H, m), 3.23-3.17 (2H, m), 2.85-2.76 (2H, m), 2.59 (3H, s), 2.46-2.45 (2H, m), 2.07-1.98 (4H, m), 1.90-1.87 (2H, m), 1.80-1.70 (6H, m), 1.42 (9H, s). MS calcd for $C_{33}H_{45}N_4O_2$ $(M+H)^+$ 529, found 529.

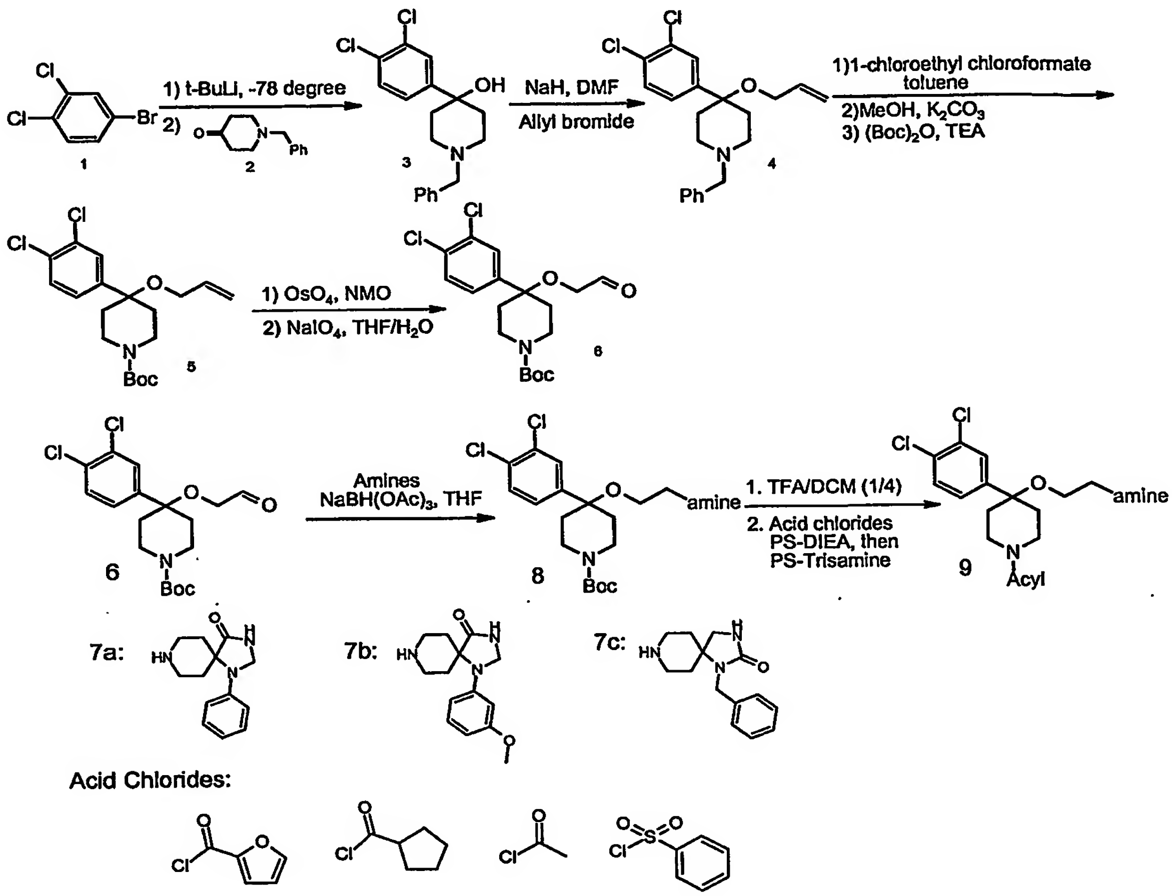
Example 707



^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.90 (1H, s), 7.51 (1H, s), 7.46-7.35 (7H, m), 6.99-6.94 (1H, m), 6.46 (1H, s), 4.49-4.43 (1H, m), 4.14-4.11 (2H, m), 3.48 (2H, s), 3.28 (2H, s), 2.56 (3H, s), 2.40-2.34 (4H, m), 2.19 (2H,

broad s), 1.93-1.85 (5H, m), 1.63-1.57 (5H, m). MS calcd. for $C_{33}H_{39}N_4O_2$ $(M+H)^+$ 523, found 523.

O-linked piperidines were synthesized according to the scheme depicted below.



Synthesis of 3 in the scheme for O-linked piperidines:

t-BuLi (31.2 mL, 1.7 M in pentane, 53.1 mmol) was added to Et_2O at –78°C, followed by 1-bromo-3,4-dichlorobenzene (3.4 mL, 26.6 mmol) dropwise. The content was stirred at -78°C for another 5 mins before 2 (4.92 mL, 26.6 mmol) was added. It was stirred and gradually warmed up to r.t. overnight. Water was added. The mixture was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered and concentrated to afford 9 g product as light brown oil (100% yield). ^{1}H NMR

(400 MHz, $CDCl_3$) δ[ppm]: 7.62 (1H, d, J=2.2 Hz), 7.39 (1H, d, J=8.4 Hz), 7.36-7.30 (5H, m), 7.28-7.24 (1H, m), 3.58 (2H, s), 2.79 (2H, d, J=11.4 Hz), 2.44 (2H, t, J=6.8 Hz), 2.11 (2H, td, J=13.4 Hz, 3.5 Hz), 1.76 (1H, s), 1.68 (2H, dd, J=13.9 Hz, 2.2 Hz).

Synthesis of 4 in the scheme for O-linked piperidines:

To a solution of 3 (9.0 g, 26.87 mmol) in DMF, NaH (2.15 g, 60% in mineral oil, 53.73 mmol) and allyl bromide (2.8 mL, 32.24 mmol) were added. The content was stirred at r.t. overnight. The reaction was quenched with water, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography with hexane/ethyl acetate (3/1) to give 7.47 g (74%) product as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.49 (1H, d, J=2.0 Hz), 7.40 (1H, d, J=8.4 Hz), 7.35-7.27 (5H, m), 7.27-7.23 (1H, m), 5.91-5.82 (1H, m), 5.28 (1H, dd, J=17.2 Hz, 1.6 Hz), 3.58-3.55 (4H, m), 2.74 (2H, d, J=11.0 Hz), 2.50-2.43 (2H, m), 1.98 (4H, d, J=3.3). LRMS: calcd. for $C_{21}H_{24}Cl_2NO$ $(M+H)^+$ 376, found 376.

Synthesis of 5 in the scheme for O-linked piperidines:

A solution of 4 (7.47 g, 199.92 mmol) in dichloroethane (120 mL) was cooled to 0 °C, 1-chloroethyl chloroformate (4.22 mL, 39.16 mmol) was added dropwise. The content was stirred at 0 °C for 15 mins and then heated to reflux for 1 hr. The solvent was removed under reduced pressure. The residue was redissolved in MeOH and the content was refluxed for 1 hr. After cooling to r.t., water and ethyl acetate were added (saw precipitate). The content was filtered to give crystalline pale-white solid. To a suspension of the solid in THF (150 mL), triethyl amine (8.35 mL, 60 mmol) and $(Boc)_2O$ were added. The content was stirred at r.t overnight. Water (100 mL) and brine (100 mL) were added. The mixture was extracted with ethyl acetate. The combined organic layer was washed with 0.1 N NaOH (2x), dried over sodium sulfate, filtered and concentrated. Flash column chromatography with hexane/ethyl acetate (9/1) gave 3.19 g product as colorless oil (42% yield). ^1H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.45 (1H, d, J=2.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.22 (1H, dd, J=8.4 Hz, 2.2 Hz), 5.90-5.80 (1H, m), 5.27 (1H, dd, J=17.2

Hz, 1.6 Hz), 5.14 (1H, dd, J=10.5 Hz, 1.3 Hz), 3.99 (2H, d, J=13.0 Hz), 3.58 (2H, d, J=5.1 Hz), 3.18 (2H, d, J=9.2 Hz), 1.98 (2H, d, J=12.7 Hz), 1.80 (2H, td, J=13.2 Hz, 5.6 Hz), 1.46 (9H, s). LRMS: calcd. for $C_{19}H_{26}Cl_2NO_3$ $(M+H)^+$ 386, found 386.

Synthesis of 6 in the scheme for O-linked piperidines:

To a solution of 5 (3.19 g, 8.29 mmol) in acetone (80 mL), *t*-BuOH (20 mL) and water (20 mL) were added, followed by OsO_4 (2.5% in *t*-BuOH, 5.2 mL, 0.42 mmol). The content was stirred at r.t for 5 mins and then NMO (1.94 g, 16.6 mmol) was added. It was stirred for another 2 hrs at r.t. The reaction was quenched with saturated $NaHSO_3$ (100 mL), extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated to give 3.5 g colorless oil. To a solution of the oil in THF (100 mL), water (25 mL) was added, followed by $NaIO_4$ (4.44 g, 20.73 mmol). The content was stirred at r.t for 4 hrs. Water (100 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was washed with 1:1 water:brine, dried over sodium sulfate, filtered and concentrated to give 2.66 g product (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 9.66 (1H, s), 7.46-7.43 (2H, m), 7.24-7.22 (2H, m), 4.00 (2H, broad d, J=10.6 Hz), 3.69 (2H, s), 3.22 (2H, broad d, J=11.7 Hz), 2.03-2.00 (2H, m), 1.90-1.83 (2H, m), 1.46 (9H, s).

Synthesis of 8a in the scheme for O-linked piperidines:

To a solution of 6 (0.885g, 2.29 mmol) in THF (10 mL), amine 7a (0.792 g, 3.44 mmol) was added. The content was stirred at r.t. for 5 mins and then $NaBH(OAc)_3$ (1.214 g, 5.73 mmol) was added. The content was stirred at r.t. overnight. The reaction was quenched with saturated sodium bicarbonate solution, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. Chromatograph purification with 5%MeOH+0.5%ammonium hydroxide in methylene chloride gave 0.62 g product as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.89 (1H, s), 7.45-7.39 (2H, m), 7.26 (3H, broad s), 6.90-6.84 (3H, m), 4.72 (2H, s), 4.09-3.95 (2H, broad), 3.19 (4H, broad s), 2.87-2.63 (8H, m), 2.00-1.96 (2H, m), 1.77-1.67 (4H, m), 1.45 (9H, s). LRMS: calcd. for $C_{31}H_{41}Cl_2N_4O_4$ 603, found 603.

Synthesis of 8b in the scheme for O-linked piperidines:

0.48 g product as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.45-7.41 (2H, m), 7.29 (1H, d, J=7.5 Hz), 7.19-7.17 (1H, broad), 6.59-6.57 (1H, broad), 6.43-6.38 (2H, m), 6.25 (1H, s), 4.70 (2H, s), 4.02-3.93 (2H, broad), 3.78 (3H, s), 3.18 (4H, broad s), 2.85-2.62 (8H, m), 2.04-1.97 (2H, broad), 1.78-1.66 (4H, m), 1.46 (9H, s).LRMS: calcd. for $C_{32}H_{43}Cl_2N_4O_5$ 633, found 633.

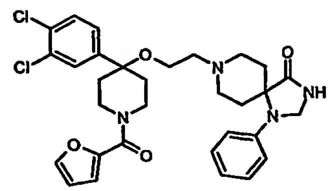
Synthesis of 8c in the scheme for O-linked piperidines:

0.56 g product as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]: 7.44 (1H, d, J=1.6 Hz), 7.36 (1H, d, J=8.5 Hz), 7.32-7.28 (4H, m), 7.22-7.17 (2H, m), 4.37 (2H, s), 3.96 (2H, broad s), 3.28 (2H, s), 3.10 (4H, broad), 2.76 (2H, d, J=11.2 Hz), 2.47 (2H, t, J=5.7 Hz), 2.04-1.91 (4H, m), 1.88-1.74 (4H, m), 1.45 (9H, s). LRMS: calcd. for $C_{32}H_{43}Cl_2N_4O_4$ 617, found 617.

Parallel Synthesis using Robins Block

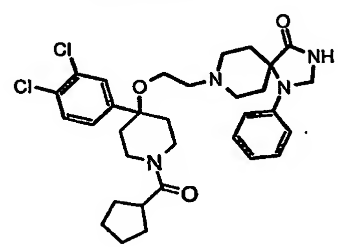
8a-8c were deprotected with TFA (1 mL) in dichloromethane (4 mL) at r.t for 20 min. Saturated sodium bicarbonate solution was added. The mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (4 mL) and added to Robins block (1 mL/each tube). To each tube were added PS-DIEA (3 eq) and acid chloride (1.5 eq.). The block was sealed and rotated overnight. It was cooled in a freezer for 15 mins and opened. PS-Trisamine (3 eq.) was added. The block was sealed and rotated for 4 hrs. The content in each tube was poured into a 24-wells filtering block and drained overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC to give the desired product.

Example 752



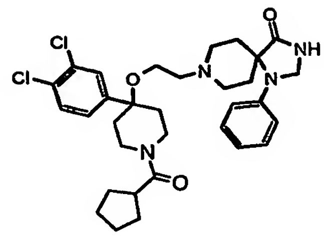
^{1}H NMR (400 MHz, CD_3OD) δ[ppm]: 8.47 (1H, s), 7.67 (2H, d, J=2.2 Hz), 7.45 (1H, dd, J=8.4 Hz, 2.0 Hz), 7.26 (2H, t, J=8.2 Hz), 7.02-6.99 (3H, m), 6.89 (1H, t, J=7.4 Hz), 6.57 (1H, dd, J=3.5 Hz, 1.8 Hz), 4.72 (2H, s), 4.39 (2H, broad s), 3.75 (2H, td, J=12.6 Hz, 2.8 Hz), 3.44-3.29 (6H, m), 3.22 (2H, t, J=5.0 Hz), 2.79 (2H, td, J=14.5 Hz, 4.8 Hz), 2.24 (2H, d, J=13.5 Hz), 2.01-1.94 (4H, m). HRMS calcd. for $C_{31}H_{35}Cl_2N_4O_4$ $(M+H)^+$ 597.2035, found 597.2045.

Example 753



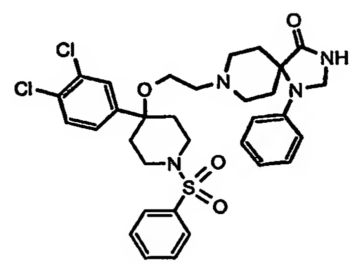
^{1}H NMR (400 MHz, CD_3OD) δ[ppm]: 8.55 (1H, s), 7.69 (1H, d, J=1.8 Hz), 7.58 (1H, dd, J=5.7 Hz, 1.8 Hz), 7.47 (1H, d, J=8.4 Hz), 7.30 (2H, t, J=8.0 Hz), 7.04 (2H, d, J=8.2 Hz), 6.92 (1H, t, J=8.2 Hz), 4.74 (2H, s), 4.45 (1H, broad d, J=12.2), 3.98 (1H, t, J=13.5 Hz), 3.72 (2H, t, J=12.1 Hz), 3.58 (1H, t, J=8.2 Hz), 3.43-3.32 (6H, m), 3.21 (2H, broad s), 3.16-3.08 (1H, m), 2.81 (2H, broad t, J=10.6 Hz), 2.32-2.15 (3H, m), 2.03-1.30 (10H, m). HRMS calcd. for $C_{32}H_{41}Cl_2N_4O_3$ $(M+H)^+$ 599.2555, found 599.2520.

Example 754



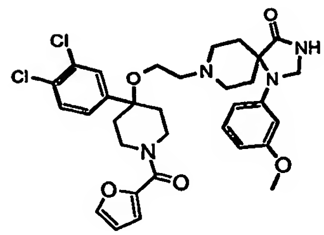
HRMS calcd. for $C_{28}H_{35}Cl_2N_4O_3$ $(M+H)^+$ 545.2084, found 545.2062. Elemental Analysis: calcd. for $C_{29}H_{37}Cl_2N_4O_5$ (formic acid salt) C 58.88%, H 6.13%, N 9.47%; found C 58.19%, H 6.13%, N 9.27%.

Example 755



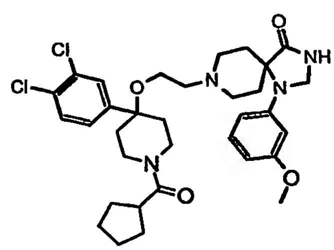
^{1}HNMR (400 MHz, CD_3OD) δ[ppm]: 8.48 (1H, broad s), 7.86-7.79 (2H, m), 7.62-7.51 (5H, m), 7.41-7.32 (3H, m), 7.06-6.95 (3H, m), 4.76 (2H, s), 3.76 (2H, d, J=19.6 Hz), 3.51-2.99 (8H, m), 2.71 (2H, t, J=11.2 Hz), 2.58 (2H, td, J=14.5 Hz, 0.6 Hz), 2.20 (2H, t, J=13.5 Hz), 2.02 (2H, td, J=12.6 Hz, 4.1 Hz), 1.75 (2H, d, J=14.6 Hz). HRMS cacld for $C_{32}H_{37}Cl_2N_4O_4S$ $(M+H)^+$ 643.1912, found 643.1926. Elemental Analysis for $C_{33}H_{38}Cl_2N_4O_4S$ (formic acid salt) calcd. C 57.47%, H 5.55%, N 8.12%; found C 56.94%, H 5.68%, N 8.04%.

Example 756



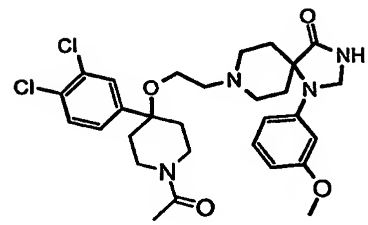
^{1}HNMR (400 MHz, CD_3OD) δ[ppm]: 8.51 (1H, broad s), 7.70 (1H, s), 7.59 (1H, d, J=8.5 Hz), 7.84 (1H, dd, J=6.5 Hz, 1.8 Hz), 7.21 (1H, t, J=8.1 Hz), 1.05 (1H, d, J=3.5 Hz), 6.68 (2H, dd, 8.3 Hz, 1.4 Hz), 6.61 (1H, dd, J=3.3 Hz, 1.7 Hz), 6.54-6.49 (3H, m), 4.72 (2H, s), 4.43 (2H, broad d, J=11.8 Hz), 3.85-3.75 (5H, m), 3.46-3.27 (8H, m), 2.85 (2H, td, J=14.5 Hz, 3.5 Hz), 2.28 (2h, d, J=13.5 Hz), 2.06-1.95 (4H, m). HRMS calcd. for $C_{32}H_{37}Cl_2N_4O_5$ $(M+H)^+$, 627.2141 found 627.2128. Elemental Analysis for $C_{33}H_{38}Cl_2N_4O_7$ (formic acid salt) calcd. C 58.84%, H 5.69%, N 8.32%; found C 58.21% H 5.76%, N 8.26%.

Example 757



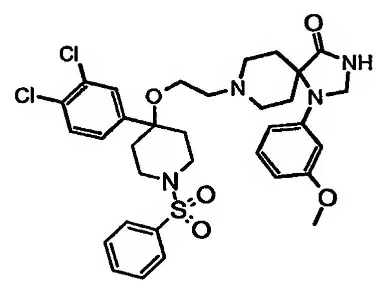
^{1}HNMR (400 MHz, CD_3OD) δ[ppm]: 8.51 (1H, broad s), 7.69 (1H, d, J=1.8 Hz), 7.58 (1H, d, J=8.4 Hz), 7.47 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.22 (1H, t, J=8.1 Hz), 6.67 (1H, broad d, J=8.1 Hz), 6.55-6.50 (4H, m), 4.73 (2H, s), 4.45 (1H, d, J=12.8 Hz), 4.00 (1H, d, J=14.4 Hz), 3.79-3.62 (5H, m), 3.55 (1H, t, J=7.1 Hz), 3.45-3.32 (6H, m), 3.22-3.11 (4H, m), 2.80 (2H, td, J=14.3Hz, 3.5 Hz), 2.22 (2H, broad d, J=11.6 Hz), 1.99-1.62 (10H, m). HRMS calcd. for $C_{33}H_{43}Cl_2N_4O_4$ $(M+H)^+$ 629.2661, found 629.2664.

Example 758



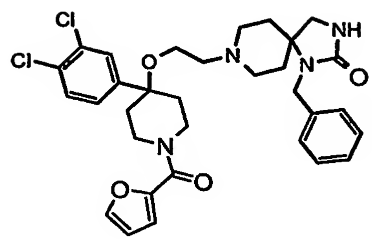
[1]HNMR (400 MHz, CD_3OD) δ[ppm]: 8.50 (1H, broad s), 7.69 (1H, d, J=1.8 Hz), 7.58 (1H, d, J=8.5 Hz), 7.47 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.22 (1H, t, J=8.1 Hz), 6.68 (1H, dd, J=8.3 Hz, 1.6 Hz), 6.55-6.50 (4H, m), 4.73 (2H, s), 4.43 (1H, d, J=13.1 Hz), 3.86-3.74 (6H, m), 3.59 (1H, t, J=10.9 Hz), 3.44-3.32 (4H, m), 3.23 (2H, s), 3.12 (1H, t, J=9.4 Hz), 2.85-2.77 (2H, m), 2.25-2.25-2.17 (5H, m), 2.04-1.75 (4H, m). HRMS calcd. for $C_{29}H_{37}Cl_2N_4O_4$ $(M+H)^+$ 575.2192, found 575.2190. Elemental Analysis calcd. for $C_{30}H_{39}Cl_2N_4O_6$ (formic acid salt) C 57.97%, H 6.16%, N 9.01%; found C 57.83%, H 6.31%, N 8.94%.

Example 759



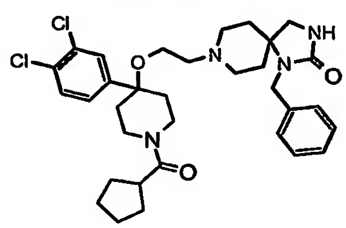
[1]HNMR (400 MHz, CD_3OD) δ[ppm]: 8.47 (1H, broad s), 7.82-7.78 (2H, m), 7.61 (1H, d, J=1.8 Hz), 7.57-7.52 (4H, m), 7.40 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.26 (1H, t, J=8.3 Hz), 6.64 (1H, dd, J=8.3 Hz, 1.8 Hz), 6.58 (1H, broad d, J=8.2 Hz), 6.50 (1H, s), 4.74 (2H, s), 3.82 (3H, s), 3.72 (2H, d, J=11.8 Hz), 3.41-3.35 (2H, m), 3.25 (2H, t, J=4.7 Hz), 3.04 (2H, broad d, J=11.0 Hz), 2.91 (2H, broad s), 2.71 (2H, t, J=10.7 Hz), 2.54 (2H, td, J=14.3 Hz, 4.8 Hz), 2.22 (2H, d, J=13.4 Hz), 2.00 (2H, td, J=12.7 Hz, 3.1 Hz), 1.73 (2H, d, J=14.3 Hz). HRMS: calcd. for $C_{33}H_{39}Cl_2N_4O_4S$ $(M+H)^+$ 673.2018, found 673.2002.

Example 760



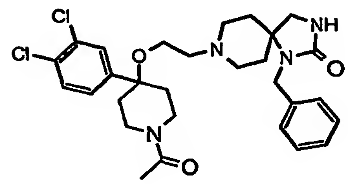
^{1}HNMR (400 MHz, CD_3OD) δ[ppm]: 8.43 (1H, broad s), 7.70 (1H, s), 7.65 (1H, d, J=1.6 Hz), 7.55 (1H, d, J=14.7 Hz), 7.41 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.36-7.29 (4H, m), 7.26-7.22 (1H, m), 7.05 (1H, d, J=3.3 Hz), 6.62-6.59 (1H, m), 4.45-4.41 (4H, m), 3.40 (2H, s), 3.33-3.27 (4H, m), 3.05 (2H, d, J=12.1 Hz), 2.80 (2H, t, J=4.8 Hz), 2.40 (2H, t, J=12.5 Hz), 2.22 (2H, d, J=13.5 Hz), 2.05-1.94 (4H, m), 1.60 (2H, d, J=13.1 Hz). HRMS: calcd. for $C_{32}H_{37}Cl_2N_4O_4$ $(M+H)^+$ 611.2192, found 611.2205. Elemental Analysis: calcd. for $C_{33}H_{39}Cl_2N_4O_6$ (formic acid salt) C 60.27%, H 5.82%, N 8.52%; found C 61.08%, H 5.91%, N 8.44%.

Example 761



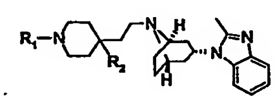
^{1}HNMR (400 MHz, CD_3OD) δ[ppm]: 7.59 (1H, d, J=2.0 Hz), 7.46 (1H, d, J=8.4 Hz), 7.37-7.27 (5H, m), 7.23-7.20 (1H, m), 4.44-4.37 (3H, m), 3.97 (1H, d, J=12.8 Hz), 3.54-3.45 (2H, m), 3.34 (2H, s), 3.23-3.18 (2H, m), 3.11-3.00 (1H, m), 2.86 (2H, broad d, J=11.4 Hz), 2.60 (2H, t, J=15.5 Hz), 2.17-2.11 (4H, m), 1.95-1.49 (14H, m). HRMS: calcd. for $C_{33}H_{43}Cl_2N_4O_3$ $(M+H)^+$ 613.2712, found 613.2723.

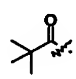
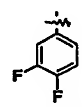
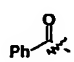
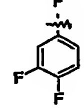
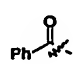
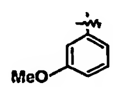
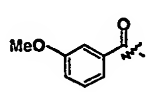
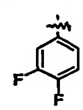
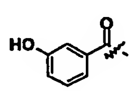
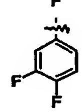
Example 762

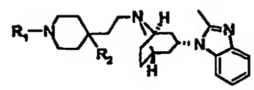


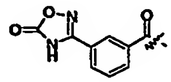
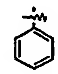
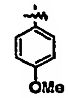
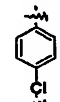
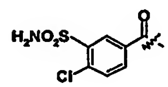
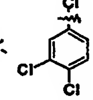
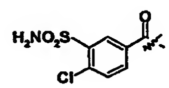
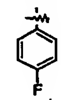
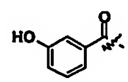
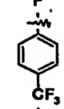
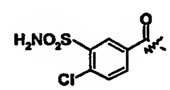
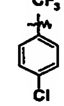
^{1}HNMR (400 MHz, CD_3OD) δ[ppm]: 8.38 (1H, broad), 7.63 (1H, d, J=1.7 Hz), 7.51 (1H, d, J=8.4 Hz), 7.41-7.25 (6H, m), 4.52 –4.41(3H, m), 3.80 (2H, t, J=11.8 Hz), 3.53 (1H, t, J=13.2 hz), 3.38 (2H, d, J=10.1 Hz), 3.26 (2H, broad s), 3.09-2.95 (4H, m), 2.83-2.67 (2H, m), 2.45-2.30 (2H, m), 2.17-1.81 (8H, m), 1.58-1.51 (2H, m). HRMS cacld for $C_{29}H_{37}Cl_2N_4O_3$ $(M+H)^+$ 559.2243, found 559.2240.

Examples 763-774 were synthesized analogously to example 16 and 703.



Example	R¹	R²	ESI-MS m/z (M+H)
763			549
764			569
765			563
766			627
767			613

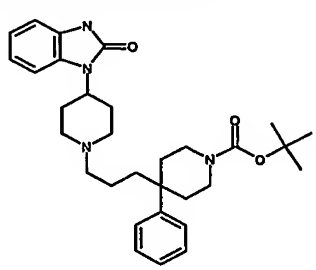


Example #	R_1	R_2	
768			617
769			543
770			548
771			716
772			665
773			645
774			681

The following compounds were synthesized using chemistry described elsewhere in this application.

Example 775

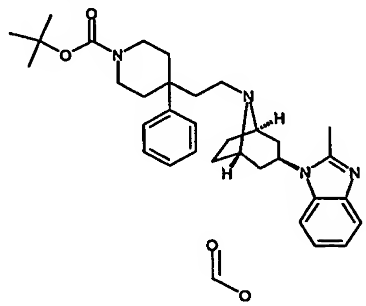
tert-butyl 4-{3-[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]propyl}-4-phenylpiperidine-1-carboxylate



^{1}H NMR (400MHz, $CDCl_3$) δ 10.43 (m, 1H), 7.32-6.98 (m, 10H), 4.28 (m, 1H), 3.65 (m, 2H), 3.09 (m, 2H), 2.87-2.84 (m, 2H), 2.37 (m, 2H), 2.18 (m, 4H), 1.95 (m, 1H), 1.70 (m, 4H), 1.54 (m, 2H), 1.41 (s, 9H), 1.14-1.00 (m, 2H). MS (electrospray +) 519.27 (M+1).

Example 776

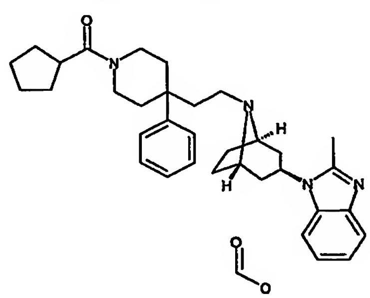
tert-butyl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate



^{1}H NMR (300MHz, methanol-d_4) δ 7.76 (m, 1H), 7.59-7.38 (m, 5H), 7.39-7.13 (m, 3H), 4.80-4.63 (m, 1H), 3.95 (m, 2H), 3.81-3.63 (m, 2H), 3.20-3.09 (m, 2H), 2.80-2.55 (m, 7H), 2.28-2.20 (m, 2H), 2.13-1.92 (m, 8H), 1.90-1.75 (m, 2H), 1.47 (s, 9H). MS (electrospray +) 529.60 (M+1).

Example 777

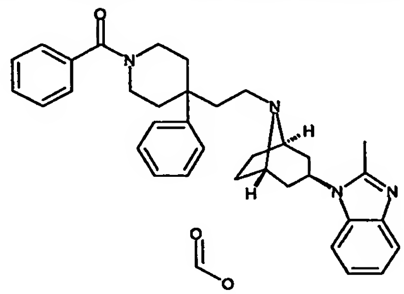
1-((1R,5S)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (300 MHz, methanol-d_4) δ 7.65 (m, 1H), 7.48-7.32 (m, 5H), 7.26-7.06 (m, 3H), 4.65 (m, 1H), 4.04-3.71 (m, 4H), 3.20 (m, 1H), 3.09-2.94 (m, 2H), 2.71-2.46 (m, 7H), 2.32-2.16 (m, 2H), 2.10-1.86 (m, 8H), 1.83-1.47 (m, 10H). HR MS (M+H) calc: 525.3593, found 525.3595, delta 0.2mmu.

Example 778

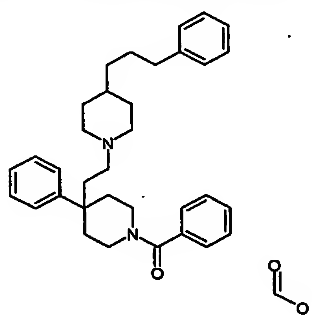
1-{(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



^{1}H NMR (300 MHz, methanol-d_4) δ 7.80 (m, 1H), 7.62-7.17 (m, 13H), 4.74 (m, 1H), 4.30-4.13 (m, 1H), 4.02 (m, 2H), 3.71-3.55 (m, 1H), 3.32 (s, 2H), 2.84-2.71 (m, 4H), 2.65 (s, 3H), 2.45 (m, 1H), 2.29-1.81 (m, 11H). HRMS (M+H) calc: 533.3280, found 533.3267, delta 1.3 mmu.

Example 779

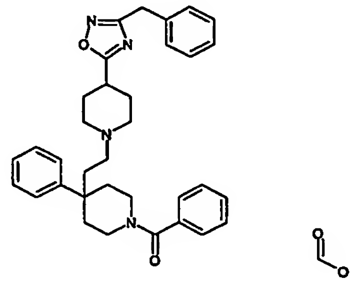
1-benzoyl-4-phenyl-4-{2-[4-(3-phenylpropyl)piperidin-1-yl]ethyl}piperidine



^{1}H NMR (300 MHz, methanol-d_4) δ 7.45-7.33 (m, 9H), 7.29-7.17 (m, 3H), 7.14-7.05 (m, 3H), 4.15 (m, 1H), 3.55 (m, 1H), 3.30-3.15 (m, 4H), 2.58-2.33 (m, 7H), 2.26-2.18 (m, 1H), 2.00-1.73 (m, 6H), 1.59 (m, 2H), 1.41 (m, 1H), 1.29-1.15 (m, 4H). HRMS (M+H) calc: 495.3375, found 495.3376, delta 0.1 mmu.

Example 780

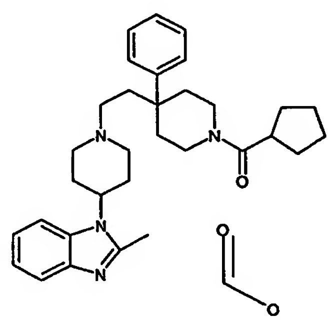
1-benzoyl-4-{2-[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]ethyl}-4-phenylpiperidine



^{1}H NMR (300 MHz, methanol-d_4) δ 7.45-7.39 (m, 9H), 7.29-7.18 (m, 6H), 4.14 (m, 1H), 4.01 (s, 2H), 3.58 (m, 1H), 3.30-3.16 (m, 3H), 3.02-2.86 (m, 3H), 2.38 (m, 1H), 2.20 (m, 4H), 2.06-1.98 (m, 2H), 1.91-1.74 (m, 6H). HRMS (M+H) calc: 535.3073, found 535.3098, delta 2.5 mmu.

Example 781

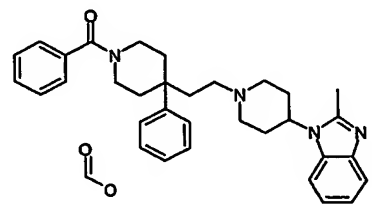
1-(1-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}piperidin-4-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d_4) δ 7.65 (m, 1H), 7.52-7.44 (m, 2H), 7.39-7.30 (m, 5H), 7.24-7.14 (m, 1H), 4.89 (m, 1H), 4.02-3.91 (m, 1H), 3.81-3.75 (m, 1H), 3.62-3.53 (m, 2H), 3.13-3.02 (m, 3H), 3.00-2.73 (m, 8H), 2.26-2.09 (m, 6H), 1.84-1.49 (m, 10H), 1.24-1.13 (m, 1H). HRMS (M+H) calc: 499.3435, found 499.3434, delta 0.1mmu.

Example 782

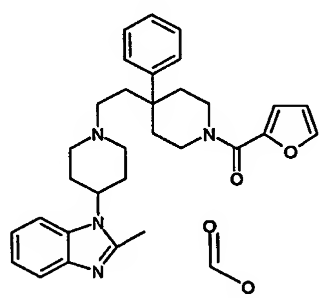
1-{1-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]piperidin-4-yl}-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d$_4$) δ 7.63 (m, 1H), 7.51-7.45 (m, 3H), 7.40-7.32 (m, 6H), 7.24-7.16 (m, 2H), 6.91 (s, 1H), 6.70 (s, 1H), 4.89 (m, 1H), 4.89 (m, 1H), 4.10 (m, 1H), 3.80 (m, 1H), 3.60 (m, 2H), 3.37-3.24 (m, 3H), 3.10 (m, 3H), 2.95-2.86 (m, 2H), 2.77 (m, 2H), 2.31 (m, 2H), 2.22-2.13 (m, 4H), 1.92-1.87 (m, 2H), 1.23-1.18 (m, 1H). HRMS (M+H) calc: 507.3126, found 507.3115, delta 1.1mmu.

Example 783

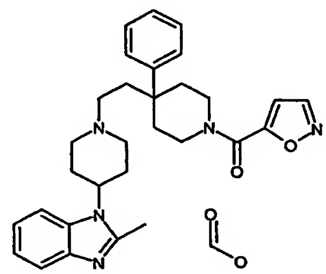
1-(1-{2-[1-(2-furoyl)-4-phenylpiperidin-4-yl]ethyl}piperidin-4-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d$_4$) δ 8.22 (m, 1H), 7.67 (m, 1H), 7.58 (s, 1H), 7.60-7.48 (m, 2H), 7.42-7.31 (m, 4H), 7.22 (m, 1H), 6.91 (m, 1H), 6.49 (s, 1H), 4.89 (m, 1H), 4.06 (m, 2H), 3.68-3.56 (m, 2H), 3.08 (m, 2H), 3.00-2.75 (m, 7H), 2.56 (s, 3H), 2.32-2.18 (m, 5H), 1.88 (m, 2H). MS (electrospray +) 523.42 (M+1).

Example 784

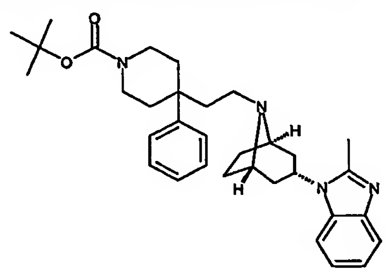
1-(1-{2-[1-(isoxazol-5-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}piperidin-4-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d_4) δ 7.64 (m, 1H), 7.46 (m, 2H), 7.41-7.27 (m, 7H), 7.24-7.10 (m, 1H), 4.88 (m, 1H), 4.07 (m, 2H), 3.61-3.49 (m, 1H), 3.20 (s, 2H), 3.11-3.00 (m, 2H), 2.93-2.84 (m, 2H), 2.79-2.71 (m, 4H), 2.30 (m, 1H), 2.21-2.09 (m, 4H), 1.92-1.75 (m, 2H), 1.21 (m, 1H). HRMS (M+H) calc: 498.2869, found 498.2845, delta 2.4 mmu.

Example 785

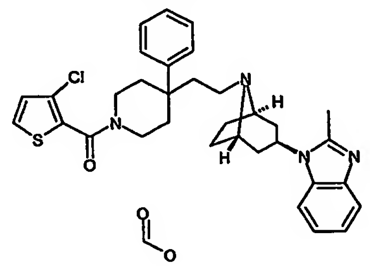
tert-butyl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 1H), 6.91-6.68 (m, 8H), 4.15 (m, 1H), 3.23-3.18 (m, 2H), 2.82-2.67 (m, 4H), 2.12 (s, 3H), 1.97-1.87 (m, 2H), 1.76-1.64 (m, 2H), 1.51-1.29 (m, 10H), 1.17-1.13 (m, 2H), 1.00 (s, 9H). MS (electrospray +) 529.61 (M+1).

Example 786

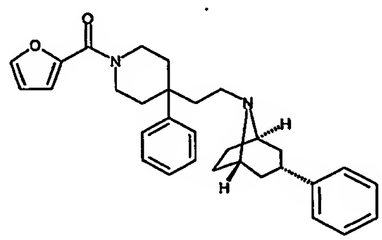
1-[(1R,5S)-8-(2-{1-[(3-chlorothien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d_4) δ 7.66 (m, 1H), 7.56-7.43 (m, 5H), 7.34-7.23 (m, 3H), 7.01 (m, 2H), 4.72 (m, 1H), 4.10 (m, 2H), 3.41-3.28 (m, 4H), 2.90 (m, 2H), 2.79 (m, 2H), 2.68 (s, 3H), 2.41-1.94 (m, 12H). HRMS (M+H) calc: 573.2455, found 573.2452, delta 0.3 mmu.

Example 787

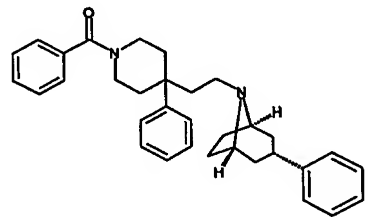
(1R,5S)-8-{2-[1-(2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-3-phenyl-8-azabicyclo[3.2.1]octane



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.31-7.00 (m, 10H), 6.86 (m, 1H), 6.38 (m, 1H), 3.98 (m, 1H), 3.48-3.27 (m, 2H), 3.12 (m, 2H), 2.96-2.86 (m, 1H), 2.38-2.15 (m, 4H), 1.98 (m, 3H), 1.86-1.76 (m, 4H), 1.60-1.50 (m, 4H), 1.29 (m, 2H). HRMS (M+H) calc: 469.2855, found 469.2858, delta 0.3 mmu.

Example 788

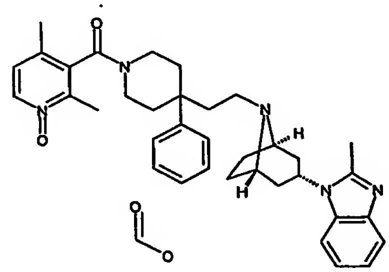
(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-3-phenyl-8-azabicyclo[3.2.1]octane



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.26 (m, 13H), 7.15 (m, 2H), 4.16-4.12 (m, 1H), 3.58 (m, 1H), 3.45 (m, 1H), 3.32-3.16 (m, 3H), 3.01 (m, 1H), 2.41-2.26 (m, 3H), 2.16-1.86 (m, 5H), 1.78-1.63 (m, 5H), 1.38-1.24 (m, 3H). HRMS (M+H) calc: 479.3062, found 479.3057, delta 0.6 mmu.

Example 789

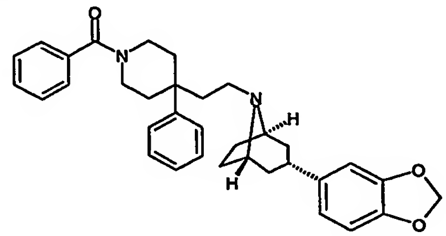
1-[(1R,5S)-8-(2-{1-[(2,4-dimethyl-1-oxidopyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (m, 1H), 7.49 (m, 1H), 7.37 (m, 5H), 7.26-7.08 (m, 4H), 4.51 (m, 1H), 4.02-3.89 (m, 2H), 3.60-3.44 (m, 2H), 3.35-3.21 (m, 4H), 3.02 (m, 1H), 2.54-2.38 (m, 4H), 2.38-2.28 (m, 3H), 2.25-2.09 (m, 3H), 2.03 (m, 2H), 1.87-1.70 (m, 8H), 1.58 (m, 2H). HRMS (M+H) calc: 578.3495, found 578.3519, delta 2.4 mmu.

Example 790

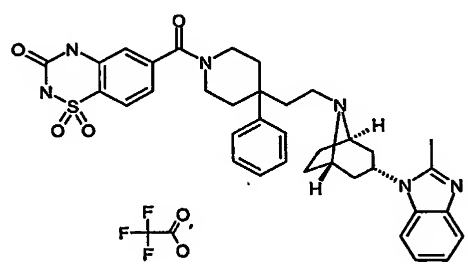
(1R,5S)-3-(1,3-benzodioxol-5-yl)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]octane



^{1}H NMR (400 MHz, $CDCl_3$) δ 73.7-7.12 (m, 9H), 6.67-6.63 (m, 2H), 5.83 (s, 2H), 4.04 (m, 1H), 3.61-3.10 (m, 5H), 2.89 (m, 1H), 2.41-2.17 (m, 3H), 2.10-1.82 (m, 6H), 1.71 (m, 1H), 1.64-1.46 (m, 4H), 1.36-1.28 (m, 2H), 1.19 (m, 2H). HRMS (M+H) calc: 523.2961, found 523.2957, delta 0.4 mmu.

Example 791

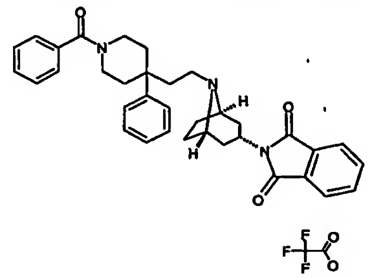
6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-dioxide



^{1}H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 1H), 7.84-7.69 (m, 3H), 7.65-7.56 (m, 1H), 7.51-7.36 (m, 6H), 7.3-7.17 (m, 2H), 5.15 (m, 1H), 4.34-3.84 (m, 5H), 3.27 (m, 2H), 2.81-2.71 (m, 5H), 2.62 (m, 2H), 2.54-2.50 (m, 2H), 2.25-2.11 (m, 8H), 1.86 (m, 2H). MS (electrospray +) 653.18 (M+1).

Example 792

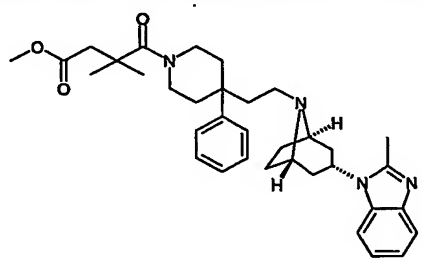
2-{(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-isoindole-1,3(2H)-dione



^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, 4H), 7.43-7.33 (m, 9H), 7.21 (m, 1H), 4.31 (m, 1H), 4.07 (m, 1H), 3.88 (m, 1H), 3.13 (m, 3H), 2.50 (s, 2H), 2.18-1.98 (m, 4H), 1.80-1.66 (m, 9H), 1.42-1.36 (m, 2H).
HRMS (M+H) calc: 548.2913, found 548.2900, delta 1.3 mmu.

Example 793

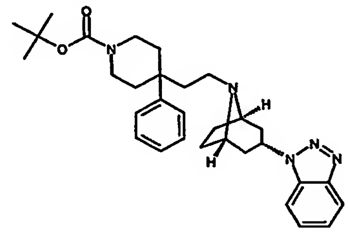
methyl 3,3-dimethyl-4-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-4-oxobutanoate



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 1H), 7.32-7.05 (m, 8H), 4.62-4.52 (m, 1H), 4.10-3.99 (m, 1H), 3.89-3.82 (m, 2H), 3.59 (m, 4H), 2.51 (m, 5H), 2.31 (m, 2H), 2.17 (m, 1H), 1.91-1.70 (m, 9H), 1.54 (m, 2H), 1.18 (m, 6H). HRMS (M+H) calc: 571.3646, found 571.3666, delta 1.8 mmu.

Example 794

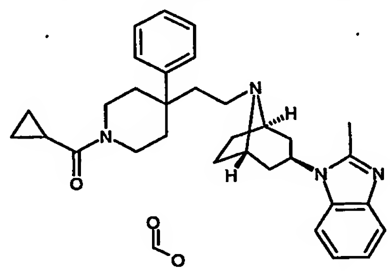
tert-butyl 4-{2-[(1R,5S)-3-(1H-1,2,3-benzotriazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (m, 1H), 7.43-7.08 (m, 8H), 4.78 (m, 1H), 3.62-3.57 (m, 2H), 3.17-3.08 (m, 4H), 2.46-2.34 (m, 2H), 2.27-2.18 (m, 2H), 2.12-1.92 (m, 4H), 1.81-1.54 (m, 8H), 1.38 (s, 9H).
HRMS (M+H) calc: 516.3339, found 516.3336, delta 0.2 mmu.

Example 795

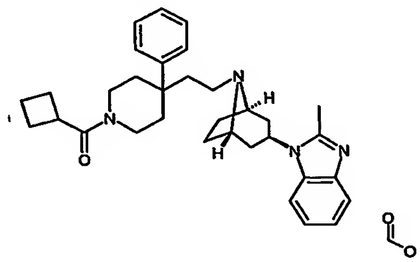
1-((1R,5S)-8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d_4) δ 7.92 (m, 1H), 7.55-7.39 (m, 5H), 7.31-7.16 (m, 3H), 4.71 (m, 1H), 4.09-3.95 (m, 4H), 3.52-3.39 (m, 1H), 3.29-3.07 (m, 2H), 2.88-2.74 (m, 4H), 2.65 (s, 3H), 2.39-1.73 (m, 12H), 0.83-0.74 (m, 4H). HRMS (M+H) calc: 497.3280, found 497.3286, delta 0.6 mmu.

Example 796

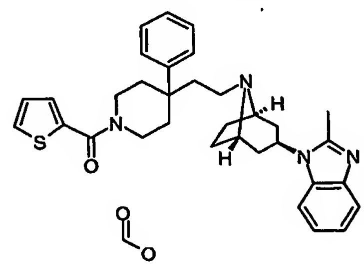
1-((1R,5S)-8-{2-[1-(cyclobutylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d$_4$) δ 8.28 (s, 1H), 7.50-7.38 (m, 5H), 7.29-7.13 (m, 3H), 4.69 (m, 1H), 4.10-3.93 (m, 3H), 3.62-3.57 (m, 1H), 3.37-3.04 (m, 4H), 2.86-2.66 (m, 4H), 2.60 (s, 3H), 2.26-1.89 (m, 14H), 1.77-1.70 (m, 3H). HRMS (M+H) calc: 511.3437, found 511.3434, delta 0.6 mmu.

Example 797

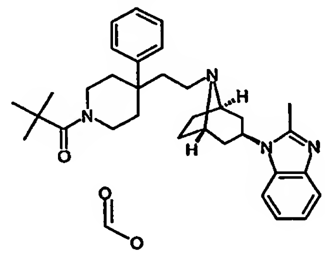
2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



^{1}H NMR (300 MHz, methanol-d$_4$) δ 7.96 (m, 1H), 7.62-7.59 (m, 1H), 7.52-7.17 (m, 9H), 7.10 (m, 1H), 4.73 (m, 1H), 4.06 (m, 4H), 3.49-3.36 (m, 2H), 2.90-2.73 (m, 4H), 2.64 (s, 3H), 2.38-1.91 (m, 12H). HRMS (M+H) calc: 539.2845, found 539.2854, delta 0.9 mmu.

Example 798

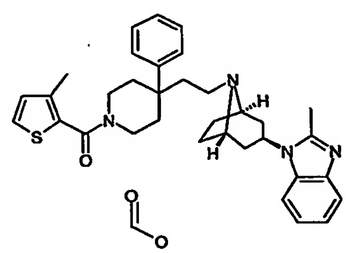
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



^{1}H NMR (400 MHz, methanol-d_4) δ 7.84 (m, 1H), 7.56-7.40 (m, 5H), 7.32-7.26 (m, 1H), 7.20 (m, 2H), 4.73 (m, 1H), 4.03 (m, 3H), 3.30-3.20 (m, 3H), 2.85-2.74 (m, 4H), 2.64 (s, 3H), 2.32-2.29 (m, 2H), 2.20-2.11 (m, 4H), 2.03 (m, 4H), 1.87-1.82 (m, 3H), 1.27 (s, 9H). HRMS (M+H) calc: 513.3593, found 513.3607, delta 1.3 mmu.

Example 799

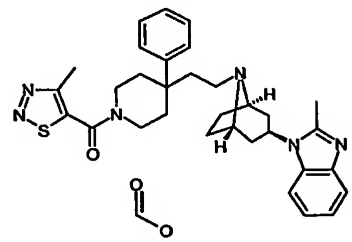
2-methyl-1-[(1R,5S)-8-(2-{1-[(3-methylthien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



MS (electrospray +) 553 (M+1).

Example 800

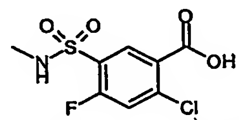
2-methyl-1-[(1R,5S)-8-(2-{1-[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



MS (electrospray +) 555 (M+1).

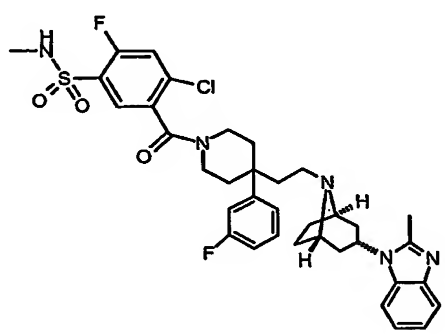
Example 802

Preparation of 2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoic acid



20.02g (73.4 mmol) of 2-chloro-3-chlorosulfonyl-4-fluorobenzoic acid was added as a solid to a cooled solution of 10.5 mL of methylamine (40% aqueous solution, 293.6mmol) in 400 mL of water. Reaction was monitored by LC/MS and complete after one hour. The reaction was acidified to pH=1 with concentrated HCl, and solid precpitated out. Product was obtained by filtration. 17.54 g obtained as a pale tan solid (89% yield). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ13.83-14.01 (br, 1 H), 8.21-8.26 (d, 1 H, J=9.11 Hz), 7.98-8.03 (q, 1 H, J=4.82), 7.88-7.92 (d, 1 H, J=9.11 Hz), 2.55-2.56 (d, 3 H, J= 4.82 Hz).

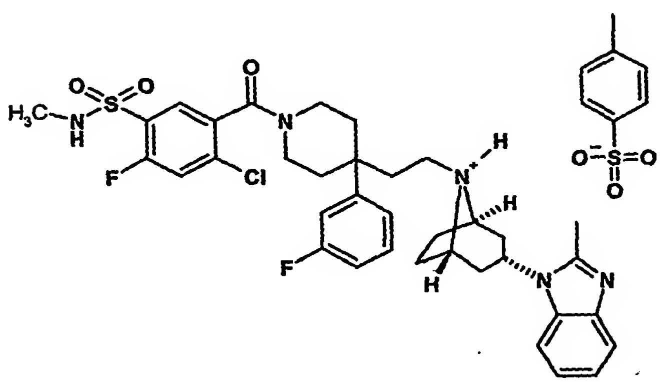
Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide



5.36g (12.0 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole, 3.20 g (12.0 mmol) 2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoic acid were combined following the general procedure in Example 5. 3.97 g recovered (47.6% yield). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 7.96-8.05 (br, 1 H), 7.75-7.94 (m, 2

H), 7.38-7.56 (m, 3 H), 7.24-7.30 (m, 2 H), 7.07-7.18 (m, 3 H), 4.48-4.60 (m, 1 H), 3.91-4.03 (m, 1 H), 3.23-3.49 (m, 6 H), 3.04-3.13 (m, 1 H), 2.52-2.60 (m, 4 H), 2.33-2.44 (m, 2 H), 2.12-2.32 (br, 2 H), 2.01-2.09 (m, 2H), 1.76-1.95 (m, 8 H), 1.60-1.66 (m, 2 H). LC/MS m/z (M+H): 696

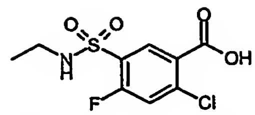
Preparation of (1*R*,5*S*)-8-{2-[1-{2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azoniabicyclo[3.2.1]octane, toluenesulfonic acid salt



The reaction vessel was charged with (1*R*,5*S*)-8-{2-[1-{2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azoniabicyclo[3.2.1]octane (5.0 g) and tetrahydrofuran (65 ml, 13 volumes). The mixture was stirred and heated to 50°C. A solution of toluenesulfonic acid monohydrate (1.4 g, 1 M in tetrahydrofuran, 1 equivalent) was added to the hot mixture. After cooling, the solid was collected by filtration, washed with tetrahydrofuran (2 x 2.5 volumes) and dried *in vacuo*. Yield 93%.

Example 803

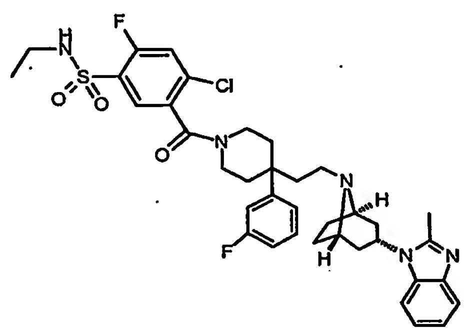
Preparation of 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid



1.023 g (3.6 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 5.49 mL (10.98 mmol) ethylamine in THF. THF was evaporated off at the completion of the reaction. Diluted with dichloromethane and extracted with 6N NaOH. Combined aqueous layers were then acidified to pH=1 with 6N HCl. Product creashes out and is collected by filtration and rinsed with water. Crude product was used in subsequent step without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13-8.16 (d, 1 H, J=7.96 Hz), 8.07-8.11 (t, 1 H, J=9.79 Hz), 7.79-7.82 (d, 1 H, J=9.79 Hz), 2.86-2.95 (m, 2H), 0.96-1.01 (t, 3 H, J=7.34 Hz).

Preparation of 4-chloro-*N*-ethyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

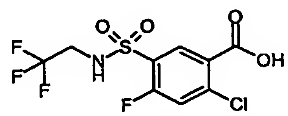


0.103 g (.23 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and .129 g (.46 mmol) 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by flash chromatography on a 0-100% gradient of 1N methanolic ammonia in ethyl acetate in ethyl acetate. 0.76 g obtained (44% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04-8.14 (m, 1 H), 7.86-7.89 (d, 1 H J=9.83 Hz), 7.72-7.79 (m, 3 H), 7.41-7.51 (m, 3 H), 7.21-7.26 (m, 2 H), 7.09-7.15 (m, 1 H), 5.00-5.11 (m, 1 H), 4.03-4.14 (m, 2 H), 3.87-3.99 (m, 1 H), 3.19-3.38 (m, 2 H), 2.96-3.05 (m, 1 H), 2.85-2.94 (m, 3 H), 2.69-2.80 (m, 4 H), 2.51-2.64 (m,

2 H), 1.93-2.26 (m, 11 H), 1.73-1.88 (m, 2H), 0.94-1.12 (m, 3H). LC/MS m/z (M+H): 710.

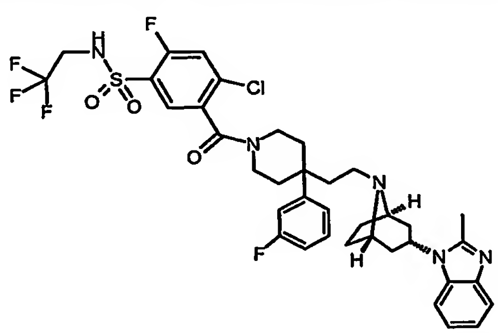
Example 804

Preparation of 2-chloro-4-fluoro-5-{[(2,2,2-trifluoroethyl)amino]sulfonyl}benzoic acid



4.997 g (18.3 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid, 2.90 g (27.5 mmol) $NaHCO_3$ were dissolved in 50 mL water. 1.45 mL (18.3 mmol) trifluoroethylamine was added dropwise to solution. Solution was acidified to pH=1 with concentrated HCl and product was extracted into ethyl acetate. Dried over $MgSO_4$ and concentrated. 5.27 g recovered (83% yield). Crude product was used in subsequent step without further purification. ^1H NMR (300 MHz, DMSO-d_6) δ 9.22-9.37 (dt, 1 H, J=6.44, 30.24 Hz), 7.80-7.92 (dd, 1 H, J=9.91, 25.78 Hz), 4.04-4.16 (m, 1H), 3.77-3.90 (m, 1 H).

Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide

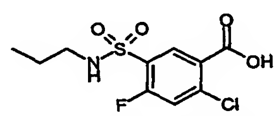


8.792 g (19.7mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 6.59 g (19.7 mmol) 2-chloro-5-[(2,2,2-trifluoroethylamino)sulfonyl]-4-fluorobenzoic acid were combined following the HATU general procedure in Example 5. This

compound was purified by flash chromatography on a 0-100% gradient of 1N methanolic ammonia in ethyl acetate in ethyl acetate. 6.31 g obtained (42% yield). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.18-9.25 (br, 1 H), 7.75-7.94 (m, 2 H), 7.35-7.52 (m, 3 H), 7.22-7.28 (m, 2 H), 7.04-7.15 (m, 3 H), 4.45-4.56 (m, 1 H), 3.80-4.00 (m, 3 H), 3.20-3.43 (m, 6 H), 2.99-3.07 (m, 1 H), 2.48-2.52 (m, 3 H), 2.32-2.41 (m, 2 H), 1.97-2.29 (br, 2 H), 1.74-1.91 (m, 8 H), 1.59-1.64 (m, 2 H).

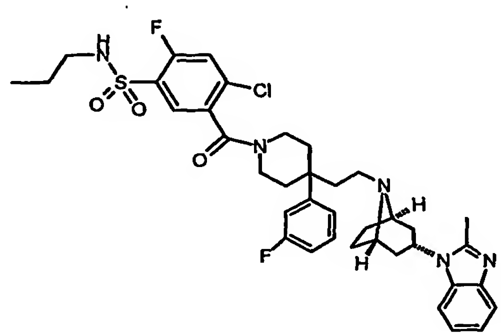
Example 805

Preparation of 2-chloro-4-fluoro-5-[(propylamino)sulfonyl]benzoic acid



2.512 g (9.2 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 2.27 mL (27.6 mmol) propylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ8.19-8.22 (d, 1 H, J= 7.84 Hz), 8.12-8.16 (t, 1 H, J=11.59 Hz), 7.85-7.88 (d, 1 H, J=9.90 Hz), 2. 80-2.87 (q, 2 H, J=6.82), 1.33-1.45 (m, 2 H), 0.77-0.82 (t, 3 H, J=7.51 Hz).

Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide

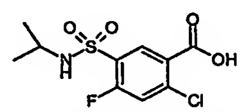


0.366 g (0.82 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.363 g (1.23 mmol) 2-chloro-4-fluoro-5-[(propylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by flash chromatography on a 0-100% gradient of 90:5:5 acetonitrile: ammonium hydroxide: water in acetonitrile. 0.24 g obtained (40% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04-8.15 (br, 1 H), 7.69-7.90 (m, 2 H), 7.32-7.52 (m, 3 H), 7.19-7.26 (m, 2 H), 7.01-7.15 (m, 3 H), 4.41-4.56 (m, 1 H), 3.86-3.98 (m, 1 H), 3.19-3.43 (m, 6 H), 2.97-3.08 (m, 1 H), 2.77-2.88 (m, 2 H), 2.44 (s, 3H), 2.28-2.41 (m, 2 H), 1.96-2.17 (m, 2H), 1.71-1.92 (m, 9 H), 1.56-1.64 (m, 2 H), 1.31-1.42 (m, 2 H), 0.73-0.81 (m, 3 H).

Example 806

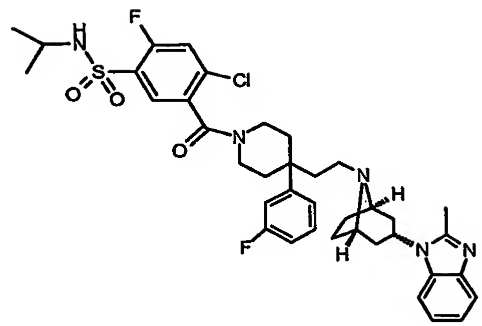
Preparation of 2-chloro-4-fluoro-5-[(isopropylamino)sulfonyl]benzoic acid



1.002 g (3.6 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 0.94 mL (10.9 mmol) isopropylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20-8.23 (d, 1 H, J=8.28 Hz), 8.12-8.17 (t, 1 H, J=7.30 Hz), 7.83-7.87 (d, 1 H, J=10.23 Hz), 3.30-3.43 (m, 1H), 0.98-1.01 (d, 6 H, J=6.34 Hz).

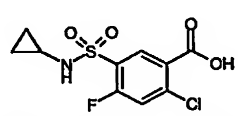
Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzenesulfonamide



0.290 g (0.65 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.288 g (0.975 mmol) 2-chloro-4-fluoro-5-[(isopropylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by reverse phase chromatography on a 0-100% gradient of 0.1% TFA in water in acetonitrile. 0.196 g obtained (42% yield).
^{1}H NMR (300 MHz, DMSO-d$_6$) δ 8.09-8.19 (m, 1 H), 7.76-7.99 (m, 2 H), 7.38-7.55 (m, 4 H), 7.25-7.31 (m, 1 H), 7.07-7.20 (m, 3 H), 4.52-4.62 (m, 1 H), 3.92-4.01 (m, 1 H), 3.29-3.43 (m, 6 H), 3.01-3.11 (m, 1 H), 2.76 (s, 1 H), 2.47-2.51 (m, 2 H), 2.36-2.45 (m, 1 H), 1.78-2.04 (m, 12 H), 1.25-1.32 (m, 3H), 0.99-1.07 (m, 6H).

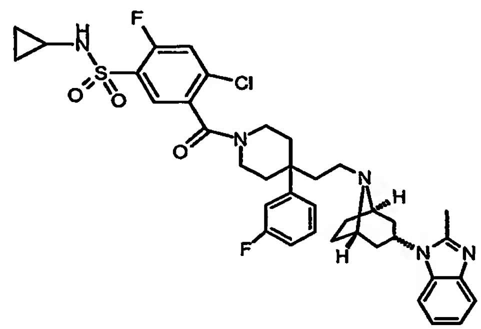
Example 807

Preparation of 2-chloro-5-[(cyclopropylamino)sulfonyl]-4-fluorobenzoic acid



1.005 g (3.6 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 0.76 mL (10.9 mmol) cyclopropylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification
^{1}H NMR (300 MHz, DMSO-d$_6$) δ8.46-8.48 (d, 1 H, J= 2.83 Hz), 8.22-8.26 (d, 1 H, J=7.69 Hz), 7.86-7.90 (d, 1 H, J=9.70), 2.23-2.32 (m, 1 H), 0.46-0.56 (m, 2 H), 0.36-0.44 (m, 2 H).

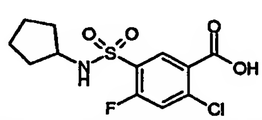
Preparation of 4-chloro-*N*-cyclopropyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



0.335 g (0.75 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.242 g (0.83 mmol) 2-chloro-4-fluoro-5-[(cyclopropylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by reverse phase chromatography on a 0-100% gradient of 0.1% TFA in water in acetonitrile. 0.231 g obtained (43% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38-8.47 (br, 1 H), 7.72-7.92 (m, 2 H), 7.33-7.51 (m, 3 H), 7.20-7.28 (m, 2 H), 7.01-7.16 (m, 3 H), 4.45-4.57 (m, 1 H), 4.06-4.12 (m, 1H), 3.87-3.98 (m, 1 H), 3.21-3.42 (m, 6 H), 2.97-3.10 (m, 1 H), 2.44 (s, 3 H), 2.23-2.42 (m, 2 H), 1.95-2.17 (m, 2 H), 1.72-1.92 (m, 8 H), 1.55-1.65 (m, 2 H), 0.34-0.53 (m, 4 H).

Example 808

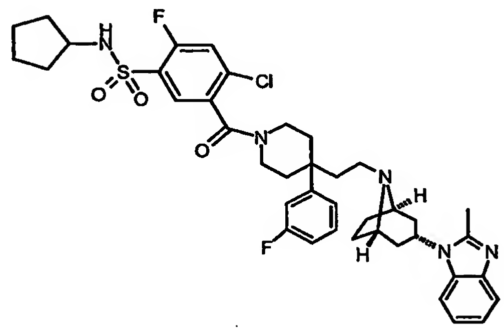
Preparation of 2-chloro-5-[(cyclopentylamino)sulfonyl]-4-fluorobenzoic acid



1.01 g (3.7 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 1.08 mL (10.9 mmol) cyclopentylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification

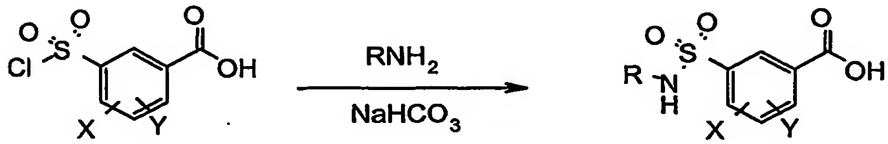
^{1}H NMR (300 MHz, DMSO-d$_6$) δ8.21-8.24 (m, 2 H), 7.84-7.88 (d, 1 H, J=10.14 Hz), ..48-3.59 (m, 1 H), 1.48-1.70 (m, 4 H), 1.28-1.46 (m, 4 H).

Preparation of 4-chloro-*N*-cyclopentyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



0.103 g (0.23 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.148 g (0.46 mmol) 2-chloro-4-fluoro-5-[(cyclopentylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by reverse phase chromatography on a 0-100% gradient of 0.1% TFA in water in acetonitrile. 0.068 g obtained (40% yield).
^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.32-9.49 (br, 1 H), 8.13-8.25 (m, 2 H), 7.73-7.91 (m, 3 H), 7.39-7.56 (m, 2 H), 7.08-7.30 (m, 3 H), 5.00-5.15 (m, 1 H), 4.03-4.16 (m, 2 H), 3.83-4.02 (m, 1 H), 3.35-3.58 (m, 2 H), 3.19-3.33 (m, 2 H), 3.16 (s, 1 H), 2.94-3.08 (m, 2 H), 2.67-2.80 (m, 6 H), 2.54-2.65 (m, 1 H), 2.02-2.26 (m, 8H), 1.72-2.01 (m, 2 H), 1.47-1.67 (m, 4H), 1.26-1.44 (m, 4 H)

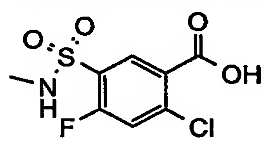
(Alkyl- or alkoxy-amino)benzoic Acids listed below were prepared using the following scheme



R= methyl, ethyl, propyl, isopropyl, cyclopropyl cyclopentyl, methoxy, ethoxy, etc.

X, Y = Cl, F,

Preparation of 2-Chloro-4-Fluoro-5-[(Methylamino)sulfonyl]benzoic Acid

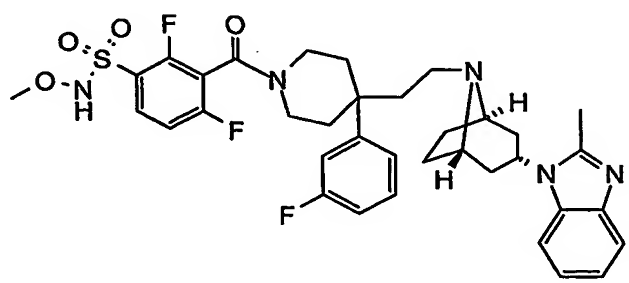


At 0 °C, to a stirred ice-water suspension (~200 mL) of 2-chloro-5-(chlorosulfonyl)-4-fluorobenzoic acid was slowly added a precooled 40% methylamine (13 mL). The reaction mixture was then stirred for 2 hours before being acidified to pH~2. The desired product was precipitated and filtered out. After being dried overnight, the pure 2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoic acid was obtained as white solid (9.8g, 100%).

The corresponding substituted aminosulfonyl benzoic acids used in this patent were prepared in the similar methods as described above.

Example 809

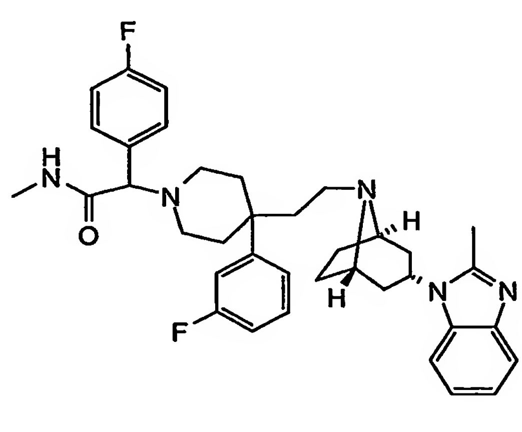
Preparation of 2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-methoxybenzenesulfonamide



2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide (11mg, 17%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (105 mg, 0.4 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (52 mg, 0.1 mmol) and methoxyamine hydrochloride (33mg, 0.4 mmol) following the coupling procedure in example 473. ^{1}H NMR (400 MHz, CD_3OD), δ 8.04 (q, J=3.3 Hz, 1 H), 7.97 (s, 2 H), 7.53 (d, J=9.6 Hz, 1 H), 7.45-7.40 (m, 2 H), 7.36-7.16 (m, 4, H), 7.01 (t, J=6.8 Hz, 1 H), 4.80-4.71 (m, 1 H), 4.20-4.19 (br, 1 H), 3.74 (d, J=10.1 Hz, 3 H), 3.57-3.42 (m, 4 H), 3.30-3.27 (m, 1 H), 2.54 (s, 3 H), 2.51-2.25 (m, 4 H), 2.09-1.93 (m, 10 H), 1.75 (d, J=7.6 Hz, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 696.2831, obsd: 696.2831.

Example 810

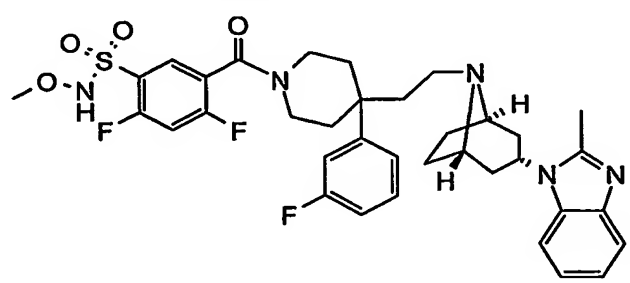
Preparation of 2-(4-fluorophenyl)-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-*N*-methylacetamide



(4-Fluorophenyl)(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (prepared from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 4-fluorophenylboronic acid following the procedure outlined in example 412. (19 mg, 0.032 mmol) was coupled with methylamine (16 µL, 2M in THF) under promotion of HATU (12 mg, 0.032mmol) The title compound was obtained as solid (12mg, 60%) after purification by flash chromatography, eluting with a gradient of 0-10%methanol in ethyl acetate. ^{1}H NMR (400 MHz, CDCl3) δ 7.66 (d, J=7.1 Hz, 1 H), 7.32-7.24 (m, 4 H), 7.19-7.12 (m, 2 H), 7.03-6.89 (m, 6H), 4.59 (br, 1 H), 3.75 (s, 1 H), 3.22 (br, 2 H), 2.84 (d, J=4.9 Hz, 3 H), 2.55 (s, 3 H), 2.52-2.47 (m, 1 H), 2.40-2.09 (m, 6 H), 1.93-1.87 (m, 7 H), 1.78-1.61 (m, 6 H). HRMS *m/z* (M+H)$^+$ calcd 612.3514, obsd 612.3530.

Example 811

Preparation of 2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide

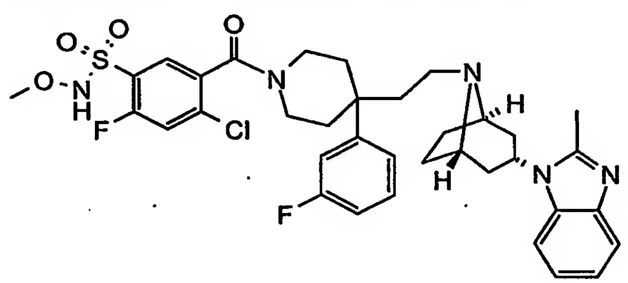


2,4-Difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzene
sulfonamide (119 mg, 43%) was obtained as solid from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-

benzimidazole dihydrochloride (244mg. 0.4 mmol) and 2,4-difluoro-5-[(methoxyamino)sulfonyl]benzoic acid (266mg, 1 mmol) and HATU (152 mg, 0.4 mmol), following the coupling procedure in example 5. ^{1}H NMR (400 MHz, CDCl3) δ 7.66 (d, J=7.3 Hz, 1 H), 7.40-7.34 (m. 1 H), 7.0 (d, J=7.3 Hz, 1 H), 7.21-7.14 (m, 2 H), 7.04-6.96 (m, 5H), 4.65-4.60 (m, 1 H), 4.23-4.20 (m, 1 H), 3.80 (s, 3 H), 3.34-3.24 (m, 6 H), 2.58 (s, 3 H), 2.45-2.37 (m, 2 H), 2.34-2.14 (m, 2 H), 2.07-1.77 (m, 12 H). HRMS *m/z* $(M+H)^+$ calcd 696.2831, obsd 696.2812.

Example 812

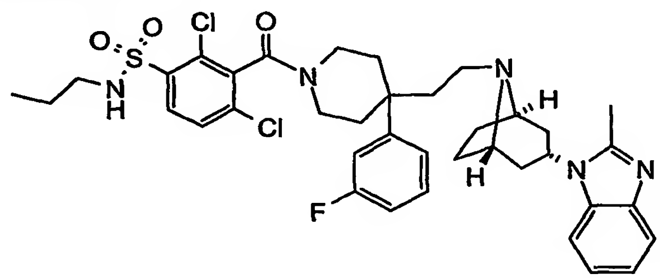
Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide



4-Chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide (170 mg, 60%) was obtained as solid from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (244 mg. 0.4 mmol) and 2-chloro-4-fluoro-5-[(methoxyamino)sulfonyl]benzoic acid (283mg, 1 mmol) and HATU (152 mg, 0.4 mmol), following the procedures outlined in example 5. ^{1}H NMR (400 MHz, CDCl3) δ 7.91 (d, J=7.2 Hz, ½ H, rotamer), 7.76 (d, J=7.1 Hz, ½ H, rotamer), 7.63 (d, J=7.5 Hz, 1 H), 7.38-7.28 (m, 3 H), 7.18-7.12 (m, 2 H), 7.08-7.04 (m, 1 H), 6.98-6.94 (m, 2 H), 4.62-4.57 (m, 1 H), 4.26-4.17 (m, 1 H), 3.78 (d, J=9.9 Hz, 3 H), 3.42-3.10 (m, 6 H), 2.55 (s, 3/2 H, rotamer), 2.54 (s, 3/2 H, rotamer), 2.42-2.32 (m, 3 H), 2.14-2.07 (m, 1 H), 1.94-1.70 (m, 10 H), 1.64-1.63 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd 712.2536, obsd 712.2546.

Example 813

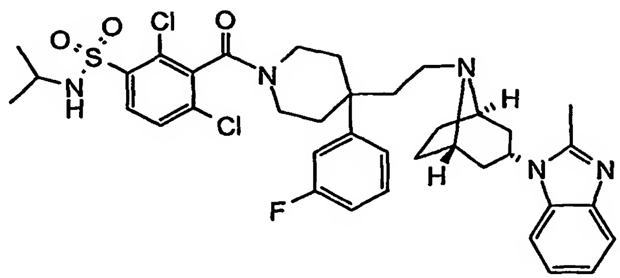
Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide



2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide (11 mg, 15%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.2 mmol), propyl amine (20 μL, 0.2mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (61 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, CD_2Cl_2), δ 8.06=8.01 (m, 1 H), 7.59-7.48 (m, 2 H), 7.42-7.34 (m, 2 H), 7.20-7.16 (m, 3 H), 7.14-6.96 (m, 2 H), 4.68 (br, 1 H), 4.23-4.20 (m, 1 H), 3.47-3.13 (m, 6 H), 2.96-2,82 (m, 4), 2.53 (s, 3/2 H), 2.41 (s, 3/2 H), 2.36-2.16 (m, 5 H), 1.98-1.84 (m, 7 h), 1.68-1.61 (m, 2 H), 1.52-1.44 (m, 2 H), 0.90-0.86 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 740.2604, obsd: 740.2589.

Example 814

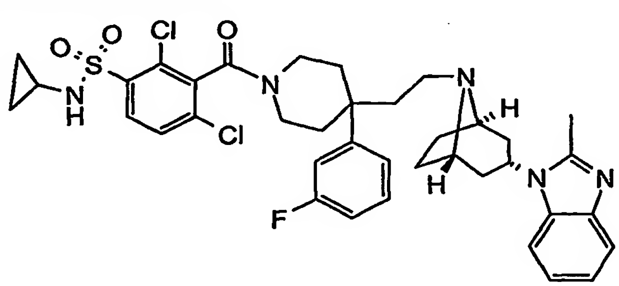
Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzenesulfonamide



2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzene
sulfonamide (13.5 mg, 18%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.2 mmol), isopropyl amine (20 μL, 0.2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (61 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, CD_2Cl_2), δ 8.07 (d, J=8.6 Hz, 1 H), 7.58-7.50 (m, 2 H), 7.42-7.35 (m, 2 H), 7.21-7.12 (m, 2 H), 7.06-6.95 (m, 3 H), 4.70-4.65 (m, 1 H), 4.23-4.19 (m, 1 H), 3.47-3.27 (m, 5 H), 3.22-3.14 (m, 2 H), 2.53 (s, 3 H), 2.46-2.32 (m, 3 H), 2.16 (br, 1 H), 1.98-1.83 (m, 11 H), 1.68 (d, J=7.7 Hz, 2 H), 1.25-1.03 (m, 6 H). HRMS *m/z* $(M+H)^+$ calcd: 740.2604, obsd: 740.2590.

Example 815

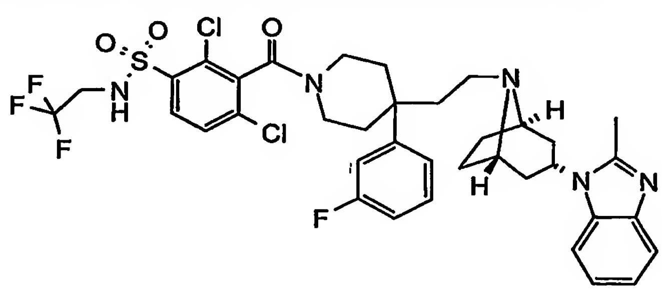
Preparation of 2,4-dichloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Dichloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene
sulfonamide (12 mg, 15%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.2 mmol), cyclopropyl amine (17 μL, 0.2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (61 mg, 0.1 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, CD_2Cl_2), δ 8.10 (d, J=7.6 Hz, 1 H), 7.59-7.52 (m, 2 H), 7.42-7.36 (m, 2 H), 7.19-7.12 (m, 3 H), 7.07-6.97 (m, 2 H), 4.67-4.63 (m, 1 H), 4.24-4.20 (m, 1 H), 3.49-3.14 (m, 6 H), 2.53 (s, 3 H), 2.44-2.33 (m, 3 H), 2.12 (br, 1 H), 1.96-1.85 (m, 11 H), 1.67-1.65 (m, 2 H), 0.74-0.67 (m, 1 H), 0.61-0.51 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 738.2448, obsd: 738.2433.

Example 816

Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide

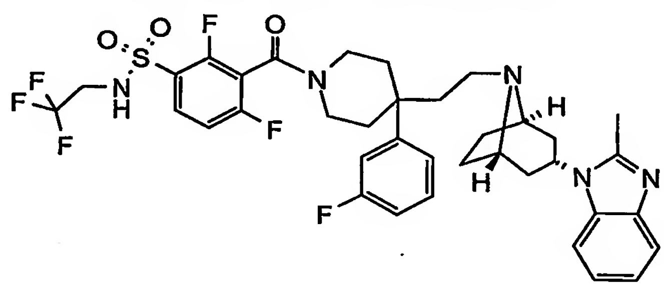


2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)
benzenesulfonamide (220 mg, 56%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (290 mg, 1 mmol), 2,2,2-trifluroethylamine (160 μL, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ^{1}H NMR (400

MHz, CD_2Cl_2), δ 8.03 (d, J=8.4 Hz, 1 H), 7.59-7.54 (m, 1 H), 7.562-7.47 (m, 1 H), 7.42-7.34 (m, 2 H), 7.19-7.12 (m, 3 H), 7.06-6.96 (m, 2 H), 4.65-4.60 (m, 1 H), 4.22-4.18 (m, 1 H), 3.79-3.69 (m, 2 H), 3.48-3.45 (m, 1 H), 3.27-3.12 (m, 3 H), 3.11-3.05 (m, 1 H), 2.52 (s, 3 H), 2.43-2.30 (m, 3 H), 2.19-2.16 (m, 2 H), 1.97-1.81 (m, 10 H), 1.66-1.62 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 780.2165, obsd: 780.2164.

Example 817

Preparation of 2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide

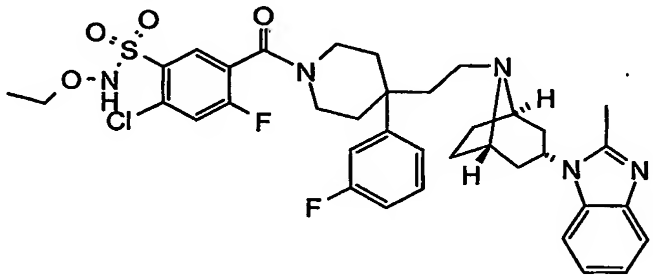


2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)

benzenesulfonamide (260 mg, 70 %) was obtained as solid from 2,6-difluro-3-(chlorosulfonyl)benzoic acid (260 mg, 1 mmol), 2,2,2-trifluroethylamine (160 μL, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ^1H NMR (400 MHz, CD_2Cl_2), δ 7.98-7.92 (m, 1 H), 7.60-7.58 (m, 1 H), 7.41-7.32 (m, 2 H), 7.22-7.20 (m, 2 H), 7.16-6.98 (m, 4 H), 4.69-4.67 (m, 1 H), 4.18 (br, 1 H), 3.80-3.62 (m, 1 H0, 3.45-3.39 (m, 3 H), 3.25-3.20 (m, 1 H), 2.55 (s, 3 H), 2.402.42 (m, 2 H), 2.42-2.40 (m, 1 H), 2.32-1.83 (m, 212 H), 1.73-1.38 (m, 2 H). HRMS *m/z* $(M+H)^+$ calcd: 748.2756, obsd: 748.2759.

Example 818

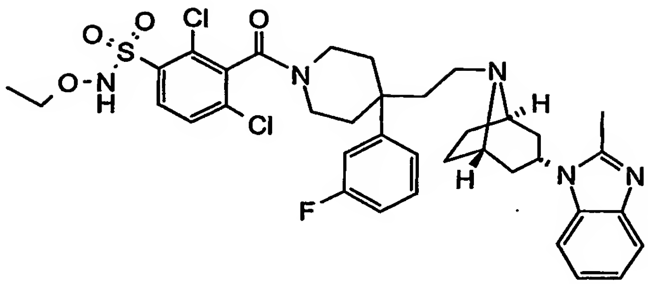
Preparation of 2-chloro-*N*-ethoxy-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



2-Chloro-*N*-ethoxy-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]
benzenesulfonamide (60 mg, 16%) was obtained as solid from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg. 0.5mmol) and 2- fluoro -4-chloro -5-[(ethoxyamino)sulfonyl]benzoic acid (297mg, 1 mmol) and HATU (190 mg, 0.5 mmol), following the procedures outlined in example 5. ^{1}H NMR (400 MHz, CD2Cl2) δ 8.15 (br, 1 H), 7.59-7.57 (m, 1 H), 7.42-7.35 (m, 3 H), 7.16-7.12 (m, 3 H), 7.07-6.97 (m, 2 H), 4.64-4.60 (m, 1 H), 4.15-4.01 (m, 4 H), 3.42-3.19 (m, 5 H), 2.53 (s, 3 H), 2.43-2.32 (m, 3 H), 2.18-2.11 (m, 1 H), 1.96-1.83 (m, 10 H), 1.66-1.64 (m, 2 H), 1.17 (t, J=6.9 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd 726.2692, obsd 726.2704.

Example 819

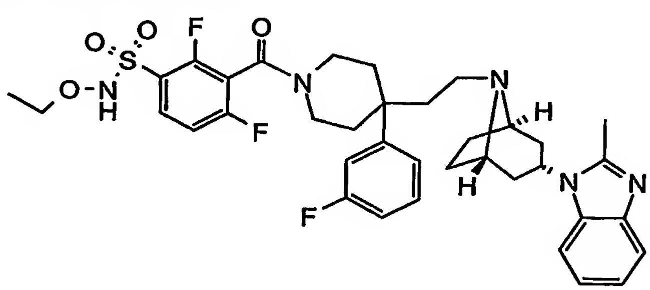
Preparation of 2,4-dichloro-*N*-ethoxy-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



2,4-Dichloro-*N*-ethoxy-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl] benzenesulfonamide (22.5 mg, 6%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (290 mg, 1 mmol), ethoxyamine hydrichloride (195 mg, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, CD_2Cl_2), δ 8.10-8.08 (m, 1 H), 7.60-7.55 (m, 2 H), 7.40-7.35 (m, 2 H), 7.18-7.12 (m, 3 H), 7.07-6.96 (m, 2 H), 4.65-4.60 (m, 2 H), 4.23-4.20 (m, 1 H), 4.06-4.00 (m, 2 H), 3.3403.12 (m, 6 H), 2.54-2.53 (m, 2 H), 2.44-2.44 (m, 4 H), 2.20-2.03 (m, 2 H), 1.97-1.84 (m, 12 H), 1.65 (d, J=7.9 Hz, 2 H), 1.18-1.14 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 742.2397, obsd: 742.2424.

Example 820

Preparation of *N*-ethoxy-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

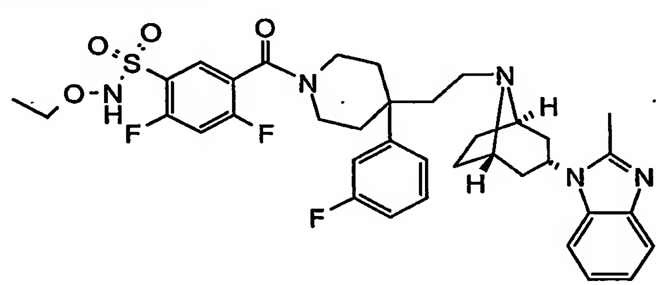


N-ethoxy-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene

sulfonamide (27.9mg, 8%) was obtained as solid from 2,6-difluoro-3-(chlorosulfonyl)benzoic acid (260 mg, 1 mmol), ethoxyamine hydrichloride (195 mg, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, CD_2Cl_2), δ 8.00-7.95 (m, 1 H), 7.58-7.56 (m, 1 H), 7.42-7.35 (m, 2 H), 7.17-7.10 (m, 4 H), 7.06-6.97 (m, 2 H), 4.65-4.60 (m, 1 H), 4.21-4.00 (m, 3 H), 3.43-3.19 (m, 5 H), 2.53 (s, 3 H), 2.44-2.32 (m, 4 H), 2.17-2.15 (m, 1 H), 1.97-1.80 (m, 10 H), 1.65 (d, J=7.8 Hz, 2 H), 1.18-1.11 (m, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 710.2988, obsd: 710.2975.

Example 821

Preparation of *N*-ethoxy-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

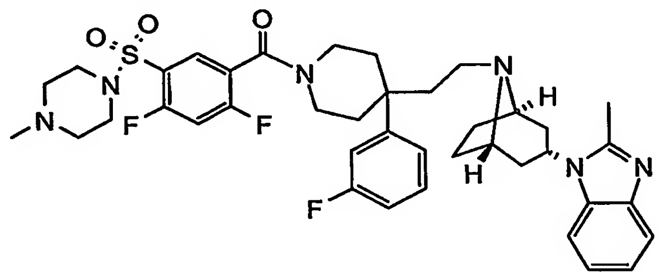


N-ethoxy-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene
sulfonamide (25mg, 7%) was obtained as solid from 2,4-difluoro-3-(chlorosulfonyl)benzoic acid (260 mg, 1 mmol), ethoxyamine hydrichloride (195 mg, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ^{1}H NMR (400 MHz, CD_2Cl_2), δ 7.96 (br, 1 H), 7.57-7.55 (m, 1 H), 7.42-7.35 (m, 2 H), 7.16-7.11 (m, 3 H), 7.08-6.96 (m, 3 H), 4.65-4.60 (m, 1 H), 4.14-4.03 (m, 3 H), 3.42-3.17 (m, 5 H), 2.52 (s, 3 H), 2.43-2.31 (m, 4), 2.13-2.09 (m, 1 H), 1.98-

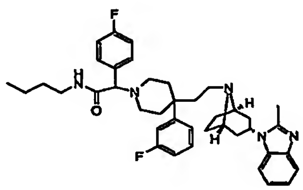
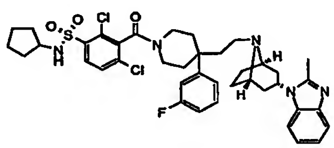
1.80 (m, 10 H), 1.65 (d, J=7.8 Hz, 2 H), 1.18 (t, J=7.0 Hz, 3 H). HRMS *m/z* $(M+H)^+$ calcd: 710.2988, obsd: 710.2975.

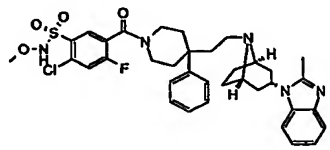
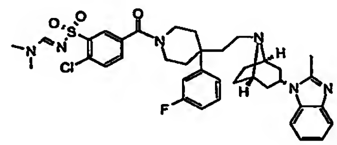
Example 822

Preparation of 1-((1*R*,5*S*)-8-{2-[1-{2,4-difluoro-5-[(4-methylpiperazin-1-yl)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-((1*R*,5*S*)-8-{2-[1-{2,4-difluoro-5-[(4-methylpiperazin-1-yl)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (170mg, 44%) was obtained as solid from 2-chloro-4-fluoro-5-[(4-methylpiperazin-1-yl)sulfonyl]benzoic acid (170 mg, 0.5 mmol) , HATU (190 mg, 0.5 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, DMSO-d_6), δ 7.93-7.88 (m, 1 H), 7.79-7.75 (m, 1 H), 7.47 (d, J=8.4 Hz, 1 H), 7.43-7.33 (m, 2 H), 7.23-7.21 (m, 3 H), 7.12-7.04 (m, 3 H), 4.50-4.46 (m, 1 H), 3.93-3.90 (m, 1 H), 3.30 (br, 4 H), 3.16-3.04 (m, 5 H), 2.43(s, 3 H), 2.32(br, 6 H), 2.13-2.12 (m, 4 H), 1.98-1.57 (m, 13 H). HRMS *m/z* $(M+H)^+$ calcd: 765.3149, obsd: 765.3165.

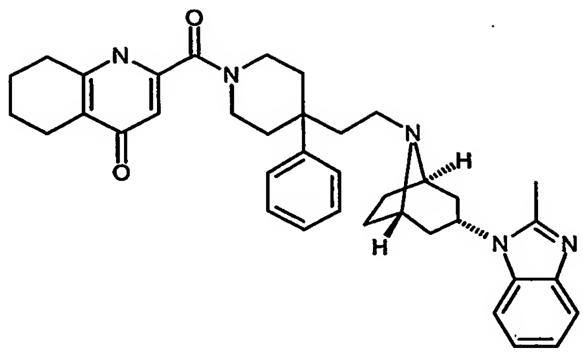
Example #	Sturcture	^{1}H NMR (400 MHz, $CDCl_3$)	HRMS m/z $(M+H)^+$
823		δ 7.66 (d, J=7.1 Hz, 1 H), 7.33-7.24 (m, 4 H), 7.19-7.12 (m, 2 H), 7.04-6.89 (m, 6H), 4.59 (br, 1 H), 3.73 (s, 1 H), 3.29-3.22 (m, 4 H), 2.55 (s, 3 H), 2.52-2.48 (m, 1 H), 2.40-2.10 (m, 6 H), 1.93-1.87 (m, 8 H), 1.79-1.61 (m, 6 H). 1.53-1.46 (m, 2, H), 1.43-1.30 (m, 2 H), 0.92 (t, J=7.3 Hz, 3 H)	**Calcd** 654.3983, **obsd** 654.3998.
824		δ 8.06 (d, J=8.4 Hz, 1 H), 7.57-7.50 (m, 2 H), 7.42-7.35 (m, 2 H), 7.20-7.12 (m, 3 H), 7.06-6.96 (m, 2 H), 470-4.65 (m, 1 H), 4.22-4.18 (m, 1 H), 3.58-3.12 (m, 6 H), 2.52 (s, 3 H), 2.46-2.36 (m, 3 H), 2.18 (br, 2 H), 1.96-1.83 (m, 11 H), 1.79-1.61 (m, 6 H), 1.47-1.38 (m, 4 H).	**calcd:** 766.2761, **obsd:** 766.2776

825		δ 8.18 (br, 1 H), 7.59-7.57 (m, 1 H), 7.43-7.33 (m, 6 H), 7.29-7.25 (m, 1 H), 7.20-7.16 (m, 2 H), 4.67-4.62 (m, 1 H), 4.18-4.15 (m, 1 H), 3.78 (s, 3 H), 3.40-3.31 (m, 4 H), 3.18-3.15 (m, 1H), 2.54 (s, 3 H), 2.46-2.34 (m, 3 H), 2.18-2.02 (m, 1 H)1.99-1.84 (m, 11 H), 1.68-1.67 (2 H).	**calcd** 694.2630, **obsd** 694.2623.
826		δ 8.21 (d, J=10 Hz, 2 H), 7.66 (d, J=10 Hz, 1 H), 7.50 (s, 2 H), 7.35-7.29 (m, 2 H), 7.20-7.13 (m, 2 H), 7.10-6.90 (m, 3 H), 4.60 (br, 1 H), 4.20 (br, 1 H), 3.55 (br, 1 H), 3.40-3.25 (m, 4 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 2.57 (s, 3 H), 2.45-2.35 (m, 2 H), 2.30-2.21 (m, 2 H), 1.95-1.89 (m, 12 H), 1.65-1.63 (m, 2 H).	**calcd:** 765.3149, **obsd:** 765.3165.

Example 827

Preparation of

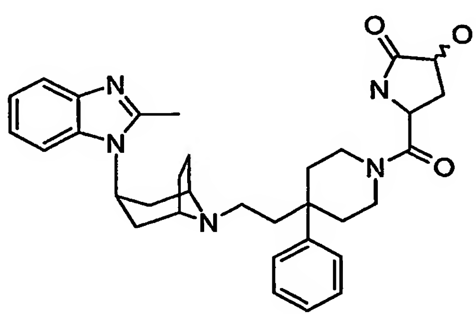
2-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-5,6,7,8-tetrahydro-4(1*H*)-quinolinone



2-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-5,6,7,8-tetrahydro-4(1*H*)-quinolinone (5.2 mg; 17% yield) was obtained as a solid from 4-oxo-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (9.66 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M-H): 602.36.

Example 828

3-hydroxy-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyrrolidinone

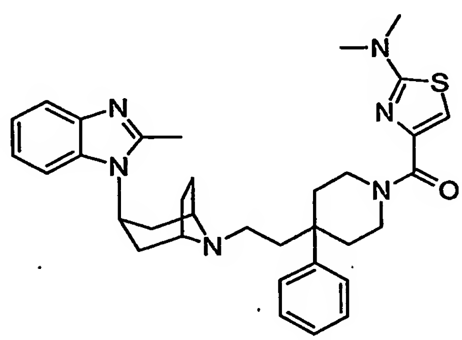


3-hydroxy-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2-pyrrolidinone (12.05 mg; 43%

yield) was obtained as a solid from 4-hydroxy-5-oxoproline (7.25 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example **5**. ES-LCMS *m/z* (M+H): 556.22.

Example 829

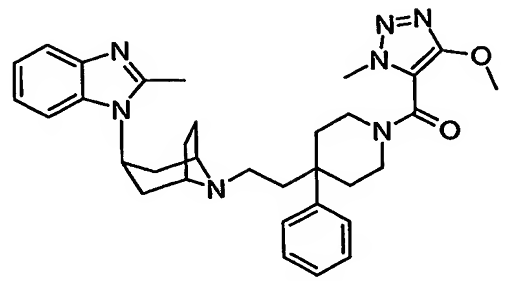
N,N-dimethyl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-thiazol-2-amine



N,N-dimethyl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-thiazol-2-amine (14.49 mg; 50% yield) was obtained as a solid from 2-(dimethylamino)-1,3-thiazole-4-carboxylic acid hydrobromide (12.65 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 583.23.

Example 830

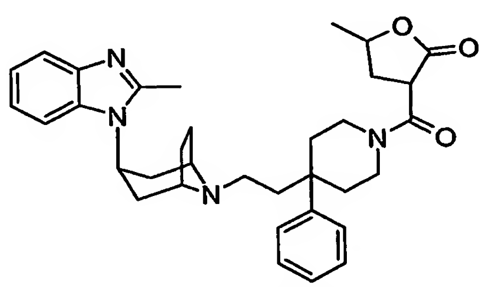
2-methyl-1-{8-[2-(1-{[1-methyl-4-(methyloxy)-1*H*-1,2,3-triazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(1-{[1-methyl-4-(methyloxy)-1*H*-1,2,3-triazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (2.99 mg; 11% yield) was obtained as a solid from 1-methyl-4-(methyloxy)-1*H*-1,2,3-triazole-5-carboxylic acid (8.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 568.20.

Example 831

5-methyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]dihydro-2(3*H*)-furanone

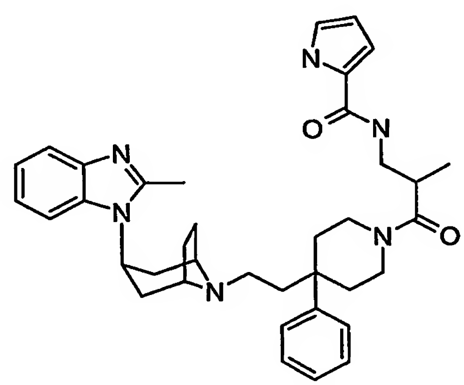


5-methyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]dihydro-2(3*H*)-furanone (10.39 mg; 36% yield) was obtained as a solid from 5-methyl-2-oxotetrahydro-3-furancarboxylic acid (7.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride

(25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 569.25

Example 832

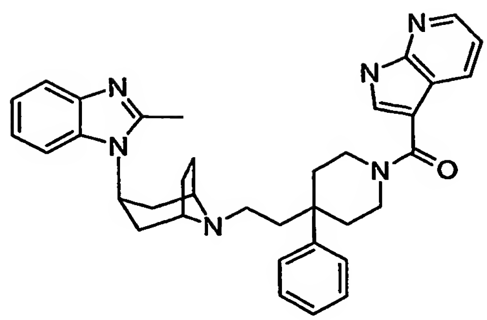
N-[2-methyl-3-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]-1*H*-pyrrole-2-carboxamide



N-[2-methyl-3-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]-1*H*-pyrrole-2-carboxamide (13.35 mg; 44% yield) was obtained as a solid from 2-methyl-3-[(1*H*-pyrrol-2-ylcarbonyl)amino]propanoic acid (7.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 607.26

Example 833

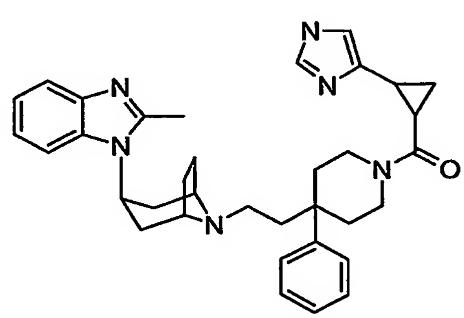
2-methyl-1-(8-{2-[4-phenyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole



2-methyl-1-(8-{2-[4-phenyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole (9.29 mg; 32% yield) was obtained as a solid from 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (8.10 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 573.21

Example 834

1-{8-[2-(1-{[2-(1*H*-imidazol-4-yl)cyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole

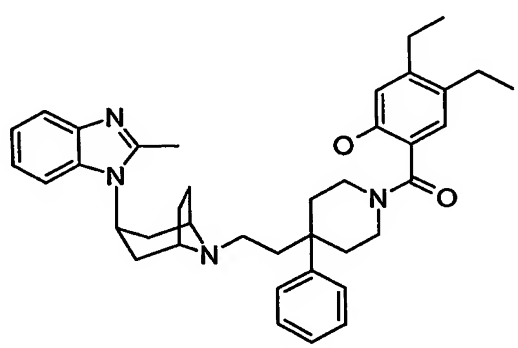


2-methyl-1-(8-{2-[4-phenyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole (12.60 mg; 45% yield) was obtained as a solid from 2-(1*H*-imidazol-4-yl)cyclopropanecarboxylic acid hydrochloride (9.43 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-

benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 563.24

Example 835

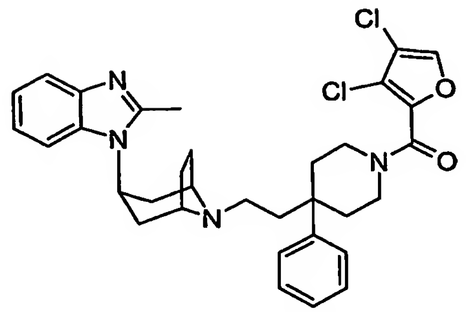
4,5-diethyl-2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol



4,5-diethyl-2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol (6.39 mg; 21% yield) was obtained as a solid from 4,5-diethyl-2-hydroxybenzoic acid (9.71 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 605.27.

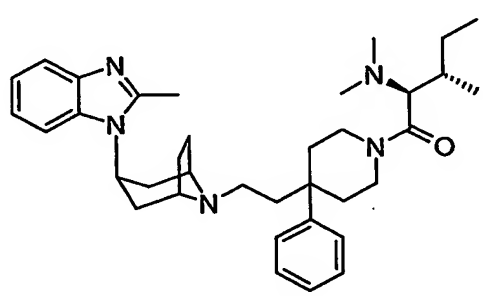
Example 836

1-[8-(2-{1-[(3,4-dichloro-2-furanyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole



1-[8-(2-{1-[(3,4-dichloro-2-furanyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (12.19 mg; 41% yield) was obtained as a solid from 3,4-dichloro-2-furancarboxylic acid (9.04 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 591.12.

Example 837
(2*S*,3*S*)-*N*,*N*,3-trimethyl-1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-pentanamine

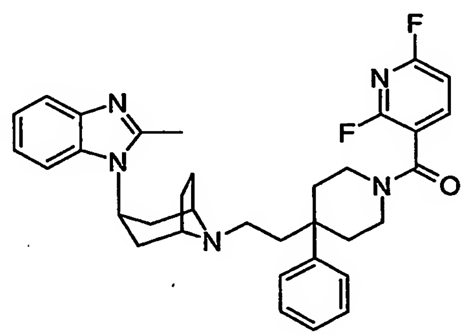


(2*S*,3*S*)-*N*,*N*,3-trimethyl-1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-pentanamine (10.05 mg; 35% yield) was obtained as a solid from *N*,*N*-dimethyl-L-isoleucine (7.96 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride # (25 mg, 0.05

mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 570.15.

Example 838

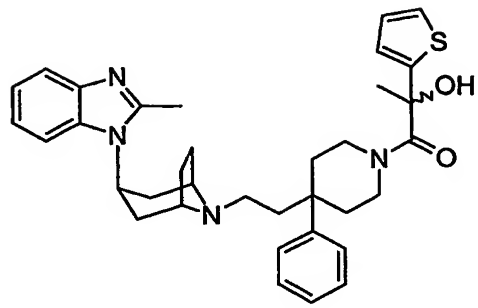
1-[8-(2-{1-[(2,6-difluoro-3-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole



1-[8-(2-{1-[(2,6-difluoro-3-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (8.35 mg; 29% yield) was obtained as a solid from 2,6-difluoro-3-pyridinecarboxylic acid (7.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 570.19.

Example 839

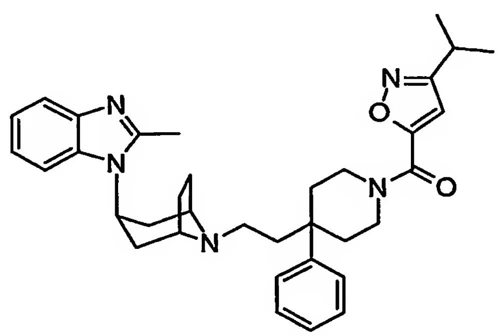
1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-(2-thienyl)-2-propanol



1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-(2-thienyl)-2-propanol (4.95 mg; 17% yield) was obtained as a solid from 2-hydroxy-2-(2-thienyl)propanoic acid (8.60mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 583.17.

Example 840

2-methyl-1-{8-[2-(1-{[3-(1-methylethyl)-5-isoxazolyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

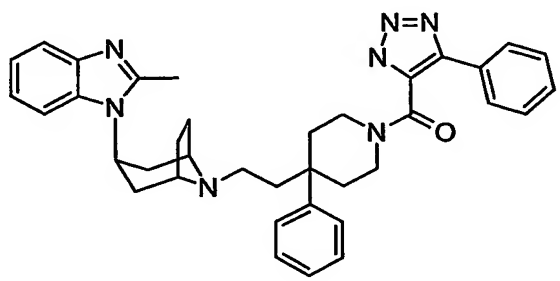


2-methyl-1-{8-[2-(1-{[3-(1-methylethyl)-5-isoxazolyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (11.29 mg; 40% yield) was obtained as a solid from 3-(1-methylethyl)-5-isoxazolecarboxylic acid hydrochloride (8.86mg, 0.05 mmol), 2-methyl-1-{8-[2-

(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 566.27.

Example 841

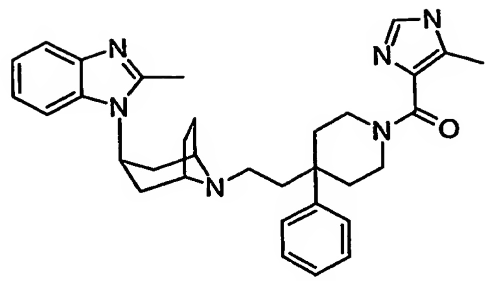
2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-1*H*-1,2,3-triazol-5-yl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole



2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-1*H*-1,2,3-triazol-5-yl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (10.29 mg; 34% yield) was obtained as a solid from 4-phenyl-1*H*-1,2,3-triazole-5-carboxylic acid hydrochloride (9.45 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 600.20.

Example 842

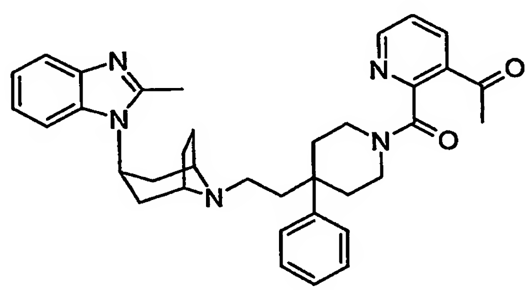
2-methyl-1-[8-(2-{1-[(4-methyl-1*H*-imidazol-5-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole



2-methyl-1-[8-(2-{1-[(4-methyl-1*H*-imidazol-5-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (9.10 mg; 34% yield) was obtained as a solid from 4-methyl-1*H*-imidazole-5-carboxylic acid (6.30 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M-H): 535.52.

<u>Example 843</u>

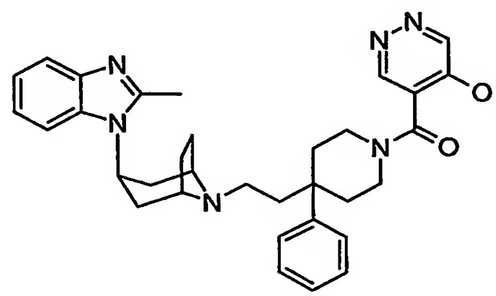
<u>1-{2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinyl}ethanone</u>



1-{2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinyl}ethanone (12.60 mg; 44% yield) was obtained as a solid from 3-acetyl-2-pyridinecarboxylic acid (9.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 576.24.

Example 844

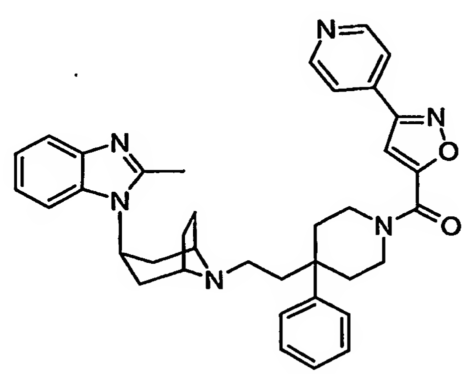
5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4-pyridazinol



5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4-pyridazinol (9.75mg; 35% yield) was obtained as a solid from 5-hydroxy-4-pyridazinecarboxylic acid (7.00 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 551.24.

Example 845

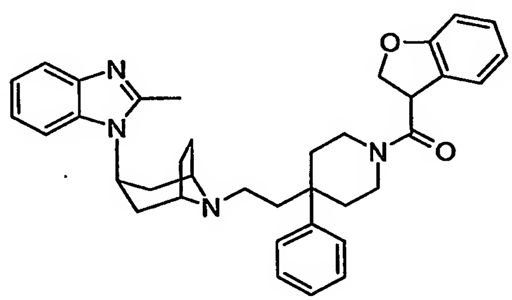
2-methyl-1-{8-[2-(4-phenyl-1-{[3-(4-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(4-phenyl-1-{[3-(4-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (15.39mg; 51% yield) was obtained as a solid from 3-(4-pyridinyl)-5-isoxazolecarboxylic acid (9.51 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.16.

Example 846

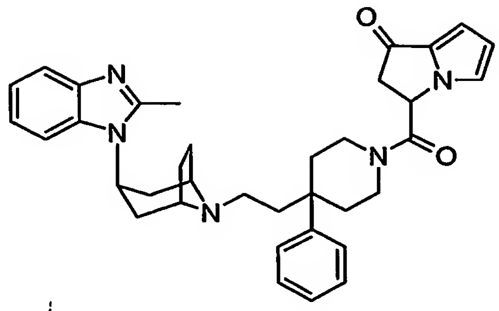
1-(8-{2-[1-(2,3-dihydro-1-benzofuran-3-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-(8-{2-[1-(2,3-dihydro-1-benzofuran-3-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (17.9 mg; 62% yield) was obtained as a solid from 2,3-dihydro-1-benzofuran-3-carboxylic acid (8.20 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 575.2.

Example 847

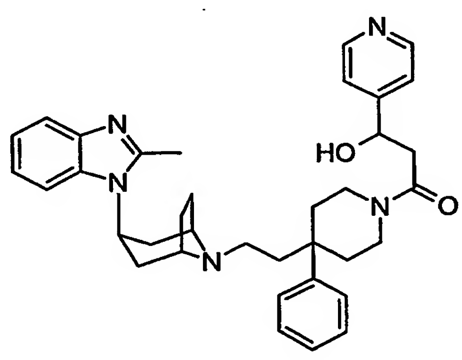
3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrol-1-one



3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrol-1-one (11.5 mg; 40% yield) was obtained as a solid from 1-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrole-3-carboxylic acid (9.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 576.22.

Example 848

3-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxo-1-(4-pyridinyl)-1-propanol

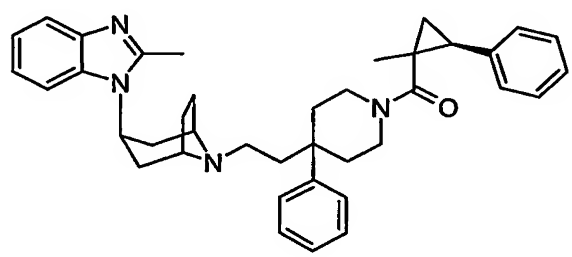


3-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxo-1-(4-pyridinyl)-1-propanol (18.59mg; 64% yield) was obtained as a solid from 3-hydroxy-3-(4-pyridinyl)propanoic acid (8.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-

azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 578.22.

Example 849

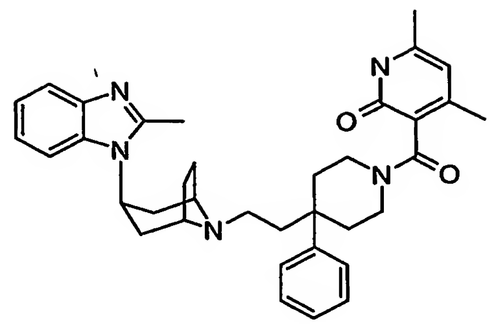
2-methyl-1-{8-[2-(1-{[(2*S*)-1-methyl-2-phenylcyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(1-{[(2*S*)-1-methyl-2-phenylcyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (18.91mg; 64% yield) was obtained as a solid from (2*S*)-1-methyl-2-phenylcyclopropanecarboxylic acid (8.81 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 587.26.

Example 850

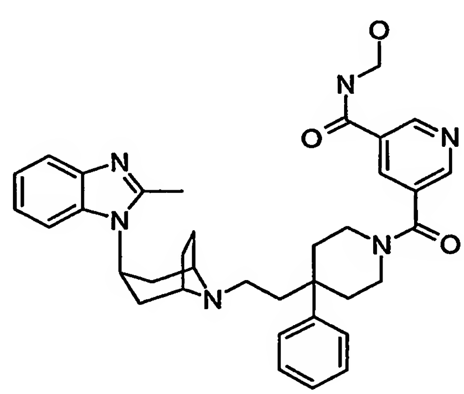
4,6-dimethyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone



4,6-dimethyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone (17.84 mg; 62% yield) was obtained as a solid from 4,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinecarboxylic acid (8.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 578.23.

Example 851

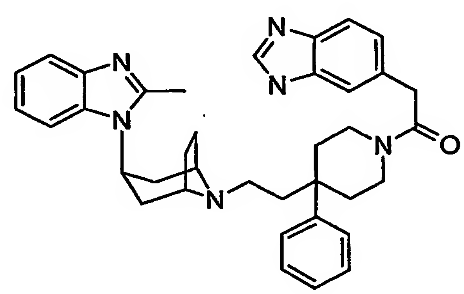
N-(hydroxymethyl)-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinecarboxamide



N-(hydroxymethyl)-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinecarboxamide (5.55 mg; 18% yield) was obtained as a solid from 5-{[(hydroxymethyl)amino]carbonyl}-3-pyridinecarboxylic acid (10.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.2.

Example 852

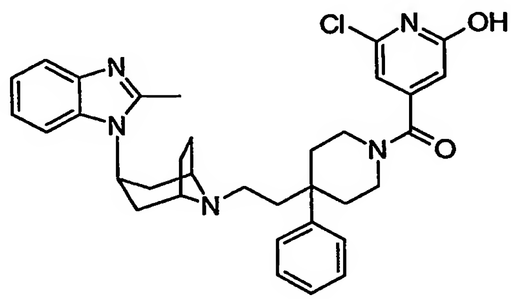
1-(8-{2-[1-(1*H*-benzimidazol-5-ylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-(8-{2-[1-(1*H*-benzimidazol-5-ylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (15.20 mg; 52% yield) was obtained as a solid from 1*H*-benzimidazol-5-ylacetic acid (10.63 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 587.18.

Example 853

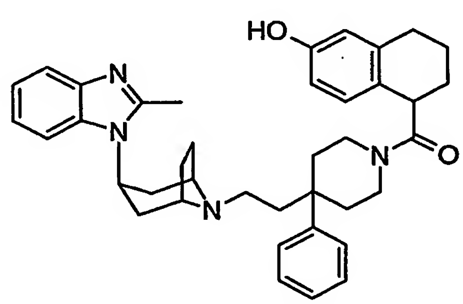
6-chloro-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone



6-chloro-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone (7.69 mg; 26% yield) was obtained as a solid from 6-chloro-2-oxo-1,2-dihydro-4-pyridinecarboxylic acid (8.67 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 584.16.

Example 854

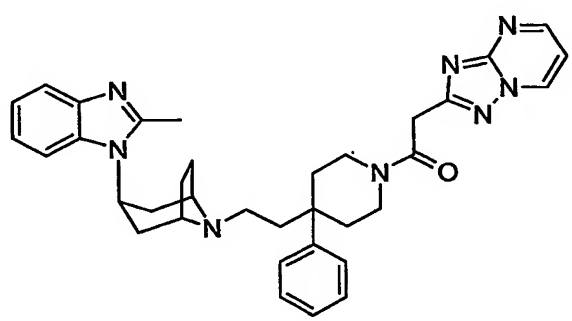
5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-5,6,7,8-tetrahydro-2-naphthalenol



5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-5,6,7,8-tetrahydro-2-naphthalenol (18.15 mg; 60% yield) was obtained as a solid from 6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenecarboxylic acid (9.61 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 603.24.

Example 855

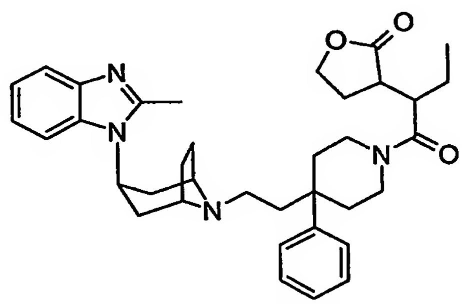
2-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl][1,2,4]triazolo[1,5-*a*]pyrimidine



2-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl][1,2,4]triazolo[1,5-*a*]pyrimidine (10.54 mg; 36% yield) was obtained as a solid from [1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylacetic acid (8.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 589.22.

Example 856

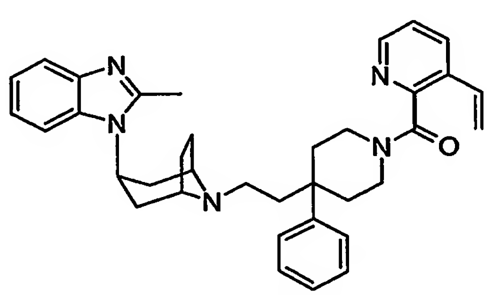
3-{1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]propyl}dihydro-2(3*H*)-furanone



3-{1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]propyl}dihydro-2(3*H*)-furanone (15.24 mg; 52% yield) was obtained as a solid from 2-(2-oxotetrahydro-3-furanyl)butanoic acid (8.60 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 583.26.

Example 857

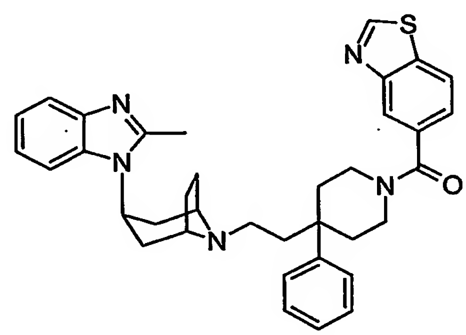
1-[8-(2-{1-[(3-ethenyl-2-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole



1-[8-(2-{1-[(3-ethenyl-2-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (5.05 mg; 18% yield) was obtained as a solid from 3-ethenyl-2-pyridinecarboxylic acid (7.54 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 560.22.

Example 858

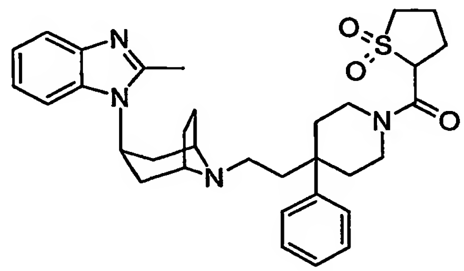
5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzothiazole



5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzothiazole (7.95 mg; 27% yield) was obtained as a solid from 1,3-benzothiazole-5-carboxylic acid (8.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 590.17.

Example 859

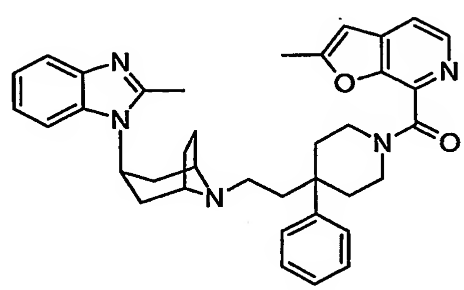
1-[8-(2-{1-[(1,1-dioxidotetrahydro-2-thienyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole



1-[8-(2-{1-[(1,1-dioxidotetrahydro-2-thienyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (8.89 mg; 31% yield) was obtained as a solid from tetrahydro-2-thiophenecarboxylic acid 1,1-dioxide (8.20 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 575.16.

Example 860

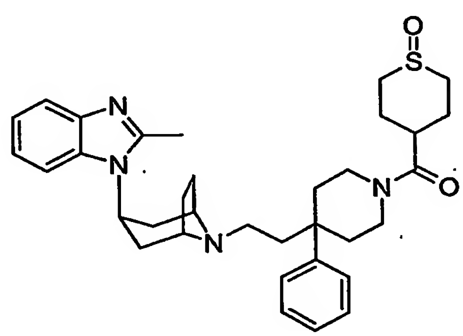
2-methyl-7-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]furo[2,3-*c*]pyridine



2-methyl-7-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]furo[2,3-*c*]pyridine (10.35 mg; 35% yield) was obtained as a solid from 2-methylfuro[2,3-*c*]pyridine-7-carboxylic acid (8.85 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 588.22.

Example 861

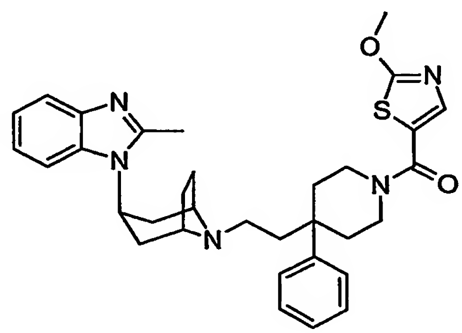
2-methyl-1-[8-(2-{1-[(1-oxidotetrahydro-2*H*-thiopyran-4-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole



2-methyl-1-[8-(2-{1-[(1-oxidotetrahydro-2*H*-thiopyran-4-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (15.85 mg; 55% yield) was obtained as a solid from tetrahydro-2*H*-thiopyran-4-carboxylic acid 1-oxide (8.11 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 573.24.

Example 862

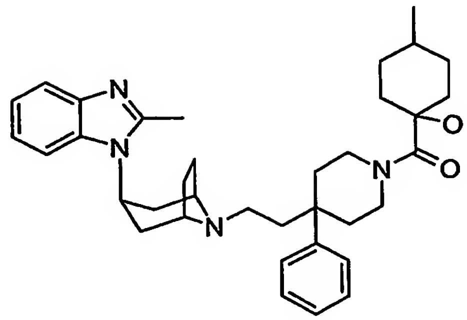
2-methyl-1-{8-[2-(1-{[2-(methyloxy)-1,3-thiazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(1-{[2-(methyloxy)-1,3-thiazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (10.75 mg; 38% yield) was obtained as a solid from 2-(methyloxy)-1,3-thiazole-5-carboxylic acid (7.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 570.21.

Example 863

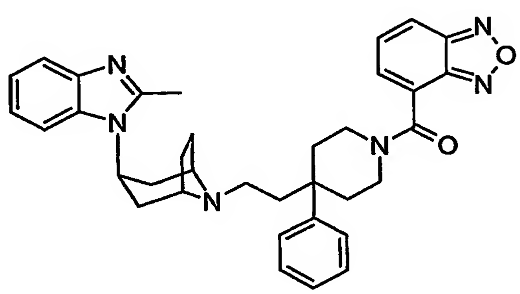
4-methyl-1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclohexanol



4-methyl-1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclohexanol (11.20 mg; 40% yield) was obtained as a solid from 1-hydroxy-4-methylcyclohexanecarboxylic acid (7.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 569.27.

Example 864

4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,1,3-benzoxadiazole

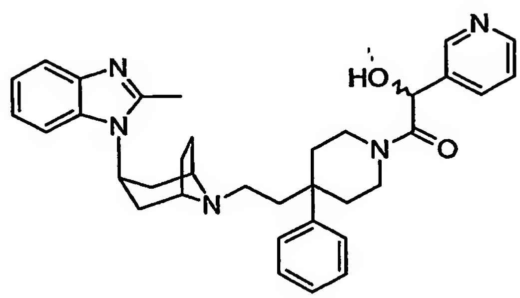


4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,1,3-benzoxadiazole (19.39 mg; 67% yield) was obtained as a solid from 2,1,3-benzoxadiazole-4-carboxylic acid (8.20 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05

mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 575.22.

Example 865

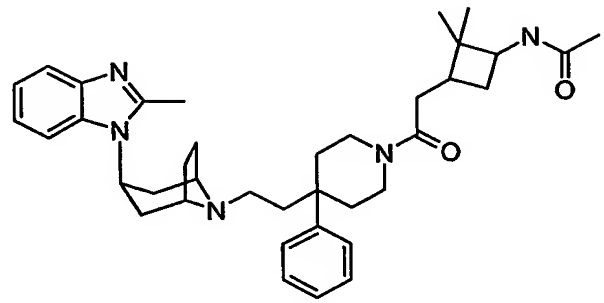
2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxo-1-(3-pyridinyl)ethanol



2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxo-1-(3-pyridinyl)ethanol (15.04 mg; 54% yield) was obtained as a solid from hydroxy(3-pyridinyl)acetic acid (7.65 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 564.16.

Example 866

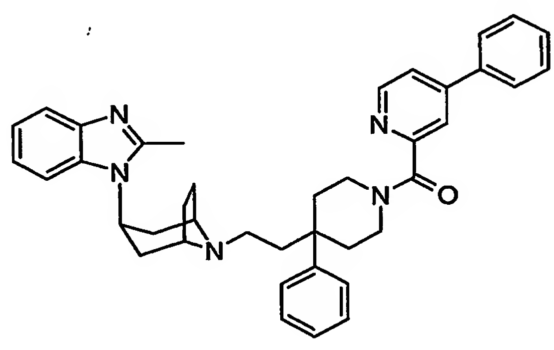
N-{2,2-dimethyl-3-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl]cyclobutyl}acetamide



N-{2,2-dimethyl-3-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-2-oxoethyl]cyclobutyl}acetamide (15.85 mg; 52% yield) was obtained as a solid from [3-(acetylamino)-2,2-dimethylcyclobutyl]acetic acid (9.96 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 610.30.

Example 867

2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-2-pyridinyl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole

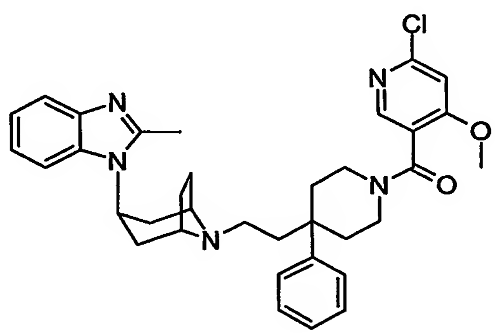


2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-2-pyridinyl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (14.94 mg; 49% yield) was obtained as a solid from 4-phenyl-2-pyridinecarboxylic acid

(9.96 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 610.20.

Example 868

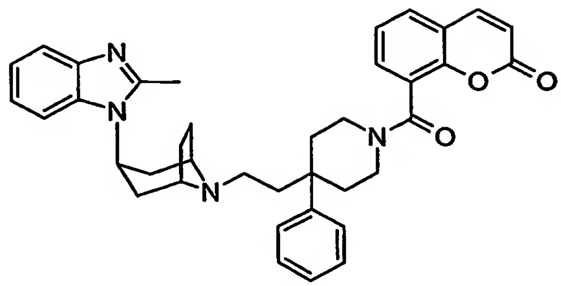
1-{8-[2-(1-{[6-chloro-4-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole



1-{8-[2-(1-{[6-chloro-4-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole (17.05 mg; 57% yield) was obtained as a solid from 6-chloro-4-(methyloxy)-3-pyridinecarboxylic acid (9.37 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 598.19.

Example 869

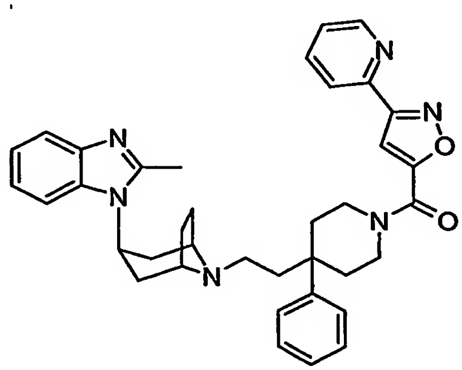
8-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2*H*-chromen-2-one



8-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2*H*-chromen-2-one (20.64 mg; 68% yield) was obtained as a solid from 2-oxo-2*H*-chromene-8-carboxylic acid (9.50 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.19.

Example 870

2-methyl-1-{8-[2-(4-phenyl-1-{[3-(2-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

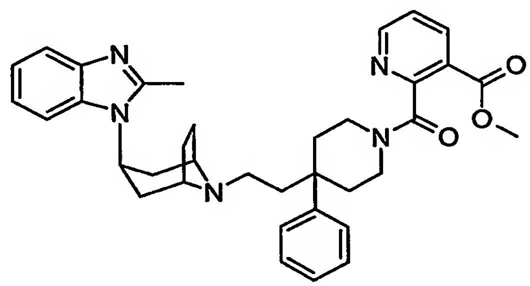


2-methyl-1-{8-[2-(4-phenyl-1-{[3-(2-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (13.15 mg; 44% yield) was obtained as a solid from 3-(2-pyridinyl)-5-isoxazolecarboxylic acid (9.50 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-

azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.22.

Example 871

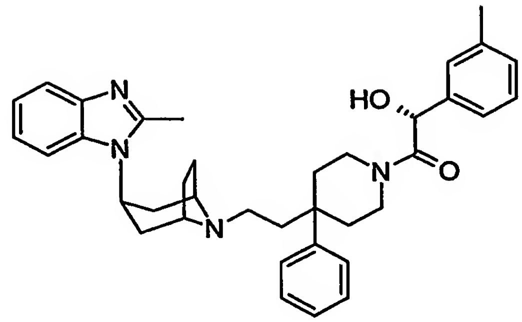
methyl 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinecarboxylate



Methyl 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinecarboxylate (8.45 mg; 28% yield) was obtained as a solid from 3-[(methyloxy)carbonyl]-2-pyridinecarboxylic acid (9. 05 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 592.21.

Example 872

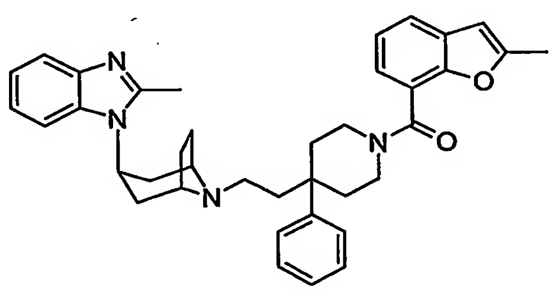
(1*R*)-2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-(3-methylphenyl)-2-oxoethanol



(1*R*)-2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-(3-methylphenyl)-2-oxoethanol (11.85 mg; 41% yield) was obtained as a solid from (2*R*)-hydroxy(3-methylphenyl)ethanoic acid (8.30 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 577.24.

Example 873

2-methyl-1-[8-(2-{1-[(2-methyl-1-benzofuran-7-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole

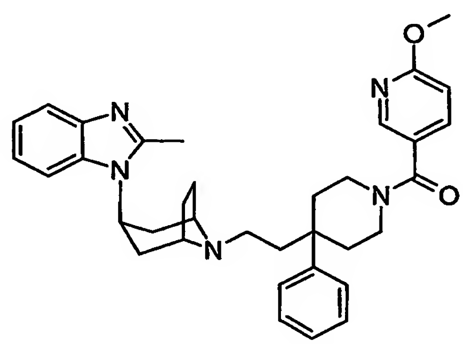


2-methyl-1-[8-(2-{1-[(2-methyl-1-benzofuran-7-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (12.30 mg; 42% yield) was obtained as a solid from 2-methyl-1-benzofuran-7-carboxylic acid (8.80 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol

mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H):587.22.

Example 874

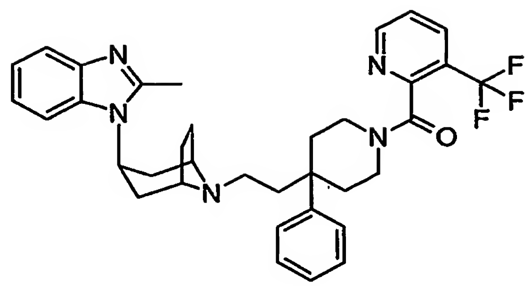
2-methyl-1-{8-[2-(1-{[6-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(1-{[6-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (13.0 mg; 43% yield) was obtained as a solid from 6-(methyloxy)-3-pyridinecarboxylic acid (9.37 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H):598.18.

Example 875

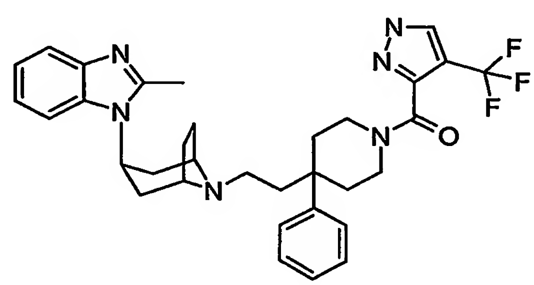
2-methyl-1-{8-[2-(4-phenyl-1-{[3-(trifluoromethyl)-2-pyridinyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(4-phenyl-1-{[3-(trifluoromethyl)-2-pyridinyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (11.89 mg; 39% yield) was obtained as a solid from 3-(trifluoromethyl)-2-pyridinecarboxylic acid (9.56 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H):602.19.

Example 876

2-methyl-1-{8-[2-(4-phenyl-1-{[4-(trifluoromethyl)-1*H*-pyrazol-3-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

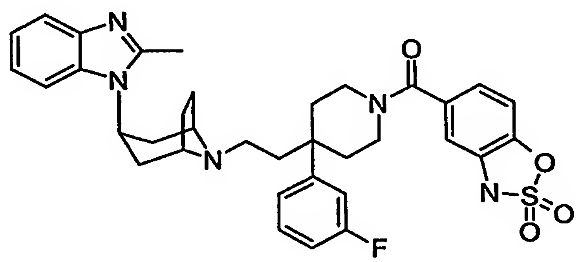


2-methyl-1-{8-[2-(4-phenyl-1-{[4-(trifluoromethyl)-1*H*-pyrazol-3-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (3.94 mg; 13% yield) was obtained as a solid from 4-(trifluoromethyl)-1*H*-pyrazole-3-carboxylic acid (9.00 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride

(25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H):591.19.

Example 877

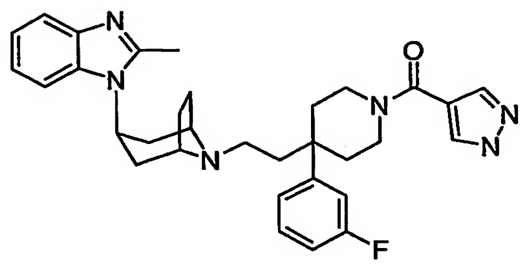
5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-3*H*-1,2,3-benzoxathiazole 2,2-dioxide



5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-3*H*-1,2,3-benzoxathiazole 2,2-dioxide
(18 mg; 27% yield) was obtained as a solid from 3*H*-1,2,3-benzoxathiazole-5-carboxylic acid 2,2-dioxide (22 mg, 0.1 mmol), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole hydrochloride (50 mg, 0.1 mmol) and HATU (38 mg, 0.1 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 644.29.

Example 878

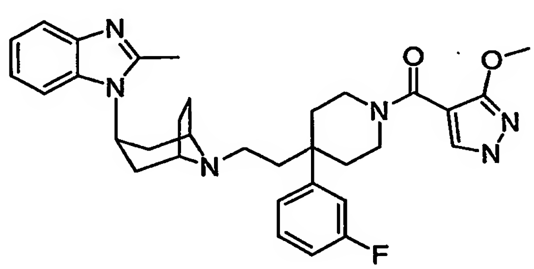
1-(8-{2-[4-(3-fluorophenyl)-1-(1H-pyrazol-4-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



1-(8-{2-[4-(3-fluorophenyl)-1-(1H-pyrazol-4-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (38 mg; 37% yield) was obtained as a solid from 1*H*-pyrazole-4-carboxylic acid (21 mg, 0.2 mmol), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole hydrochloride (100 mg, 0.2 mmol) and HATU (73 mg, 0.2 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 541.20.

Example 879

1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(methyloxy)-1*H*-pyrazol-4-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole

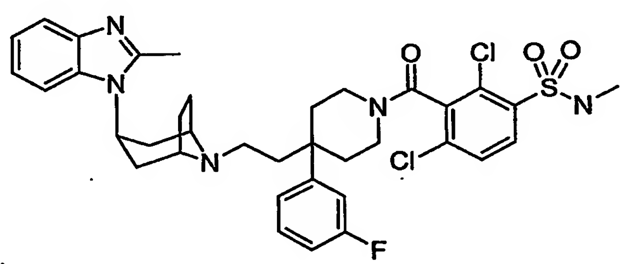


1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(methyloxy)-1-(phenylmethyl)-1*H*-pyrazol-4-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole was obtained as a crude mixture from 3-(methyloxy)-1-(phenylmethyl)-1*H*-pyrazole-4-carboxylic acid (23 mg, 0.1 mmol), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole hydrochloride (50 mg, 0.1 mmol) and HATU (38 mg, 0.1 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 661.46.

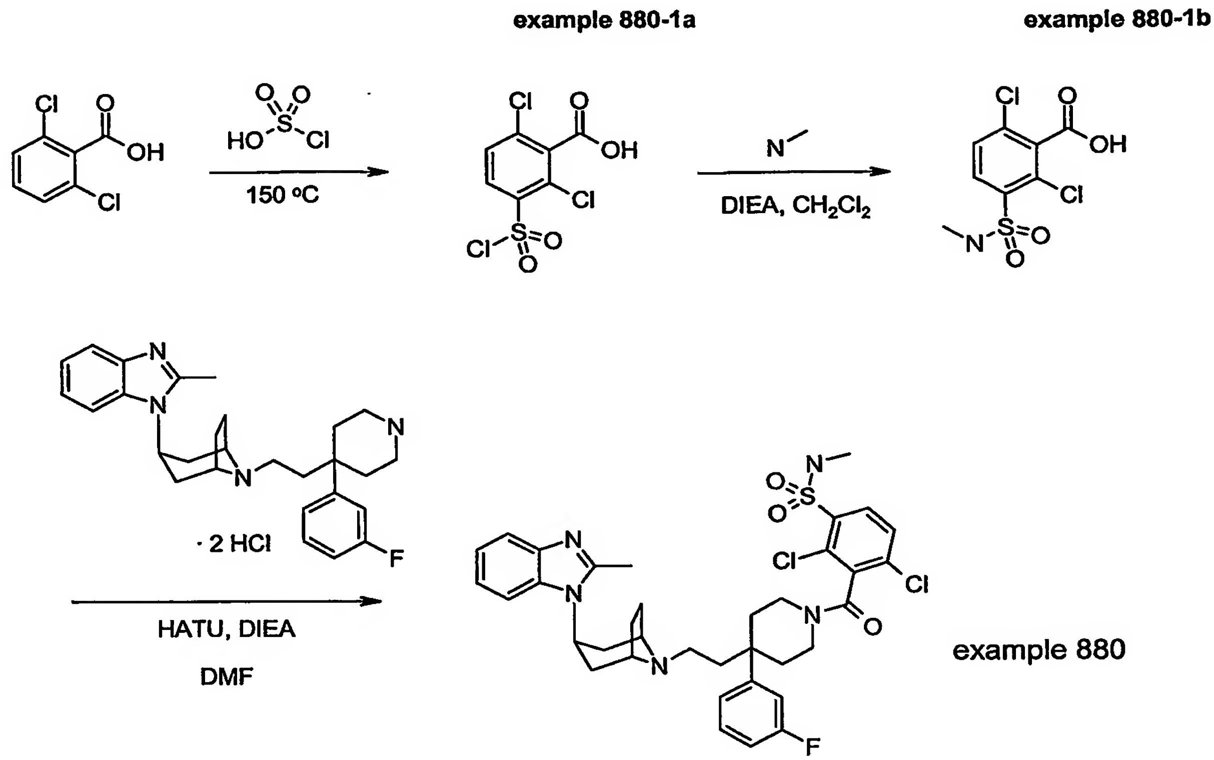
The crude mixture was then treated with $PdCl_2$ (25 mg) under 50 psi H_2 to provide 1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(methyloxy)-1*H*-pyrazol-4-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole as solid (30, 52%). ES-LCMS *m/z* (M+H): 571.24

Example 880

2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide



Example 880 was prepared according to figure below.



Synthesis of 880-1a
2,6-dichloro-3-(chlorosulfonyl)benzoic acid

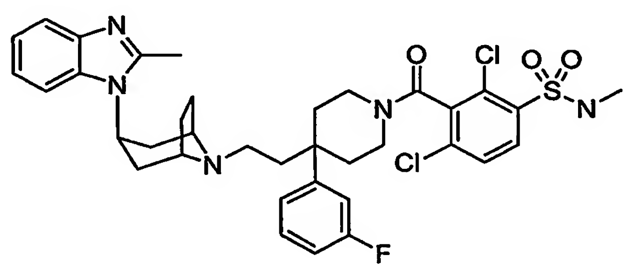
Chlorosulfonic acid was slowly added to 2,6-dichlorobenzoic acid at RT under N_2. The reaction was heated to 150 °C for 3 h, then slowly poured over ice and the product extracted into Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to give 2,6-dichloro-3-(chlorosulfonyl)benzoic acid 880-1a as a brown solid (12.9 g, 85% yield).

^1H NMR (400 MHz, DMSO) δ 13.42 (broad s, 1H), 7.88 (d, J = 8. Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H).

Synthesis of 880-1b
2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid

A mixture of 2,6-dichloro-3-(chlorosulfonyl)benzoic acid 880-1a (200 mg, 0.69 mmol, 1 equiv) and 4 mL CH_2Cl_2 was treated with diisopropylamine (248 μL, 1.38 mmol, 2 equiv) and 2M methyl amine (415 μL, 0.83 mmol, 1.2 equiv). The reaction was stirred at RT overnight, wherein the crude mixture contained 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. The mixture was carried directly into the following reaction. ES-LCMS m/z 284.0 (M-H)

Synthesis of 880
<u>2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide</u>

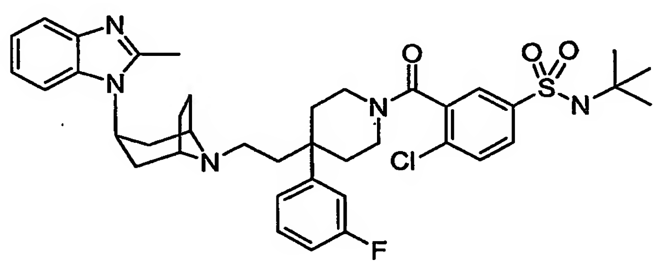


To a solution of 1-(8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (100 mg, 0.16 mmol, 1 equiv) and *N,N*-diisopropylethyl amine (117 μL, 0.66 mmol, 4 equiv) in dimethylformamide (2 mL) was added the mixture of 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. After stirring at RT for several min, *O*-(7-azabenzotriazol-1-yl)-*N N,N', N'*-tetramethyluroniumhexafluorophosphate (62 mg, 0.16 mmol, 1 equiv) was added and the reaction was stirred for 18 h. The mixture was partitioned between dichloromethane and satd. aq. $NaHCO_3$. The organic layer was dried and concentrated and the residue was purified by SiO_2 flash column chromatography (100% EtOAc → 10% 2M NH_3 in MeOH in EtOAC) to provide 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-

methylbenzenesulfonamide (example 880) as a white solid (25 mg, 22% yield).

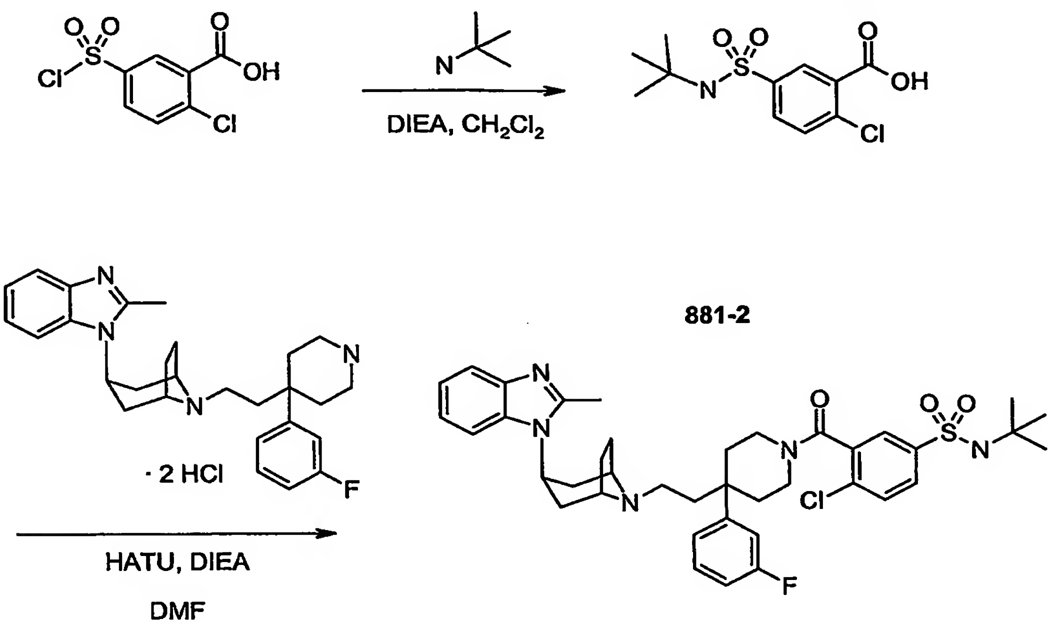
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 1H), 7.65 (m, 1H), 7.49 (m, 1H), 7.39-7.29 (m, 3H), 7.19-6.95 (m, 5H), 5.34 (m, 1H), 4.60 (m, 1H), 4.27 (m, 1H), 3.48-3.12 (m, 6H), 2.66 (m, 3H), 2.56 (m, 3H), 2.42-2.27 (m, 3H), 2.22-1.76 (m, 7H), 1.64 (m, 2H), 1.42 (m, 2H). ES-LCMS *m/z* 712.2 (M+H).

Example 881
<u>4-chloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide</u>



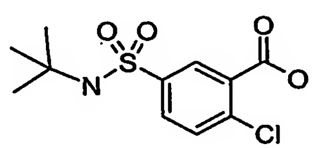
Example 881 was prepared according to figure below.

881-2a



881-2

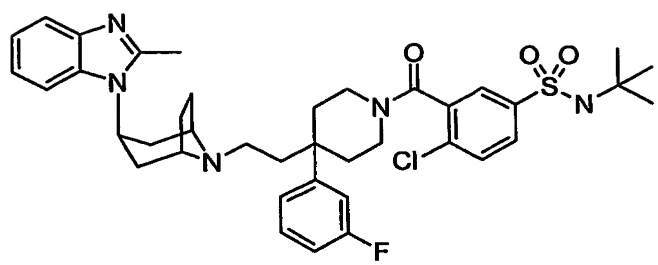
Synthesis of 881-2a
2-chloro-5-{[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid



Prepared from a mixture of 2-chloro-5-(chlorosulfonyl)benzoic acid (200 mg, 0.78 mmol, 1 euiqv) *tert*-butyl amine (98 μL, 0.94 mmol, 1.2 equiv) and DIEA (248 μL, 1.38 mmol, 2 equiv) following the general procedure for 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 881-1b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 315.2 (M+Na)

Synthesis of 881
4-chloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide

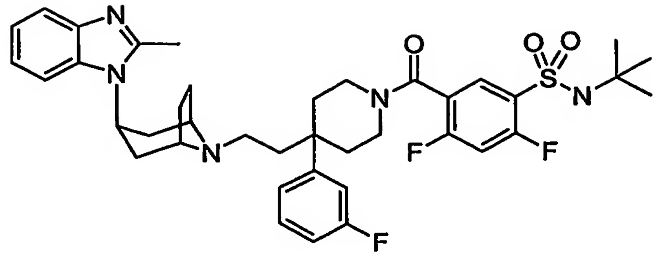


Prepared from a mixture of 2-chloro-5-{[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid
2b, 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (100 mg, 0.16 mmol, 1 equiv), DIEA (117 μL, 0.66 mmol, 4 equiv) and HATU (62 mg, 0.16 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide
example 880. The crude product was purified by column chromatography on silica gel eluting with 10% 2M NH_3 in methanol in ethyl acetate to afford 4-chloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide as a white solid (40.3 mg, 35% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.80 (m, 1H), 7.71-7.64 (m, 1H), 7.55-7.48 (m, 1H), 7.38-7.26 (m, 3H), 7.19-6.94 (m, 6H), 4.92-4.54 (m, 2H), 4.23 (m, 1H), 3.47-3.04 (m, 6H), 2.56 (m, 3H), 2.54-1.34 (m, 14H), 1.24 (m, 9H). ES-LCMS *m/z* 720.2 (M+H).

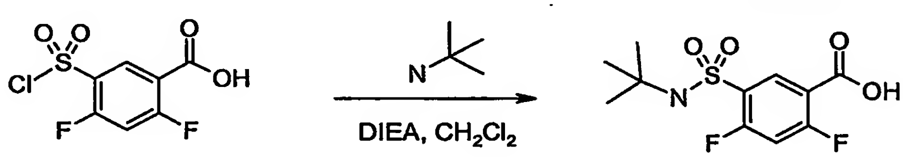
Example 882

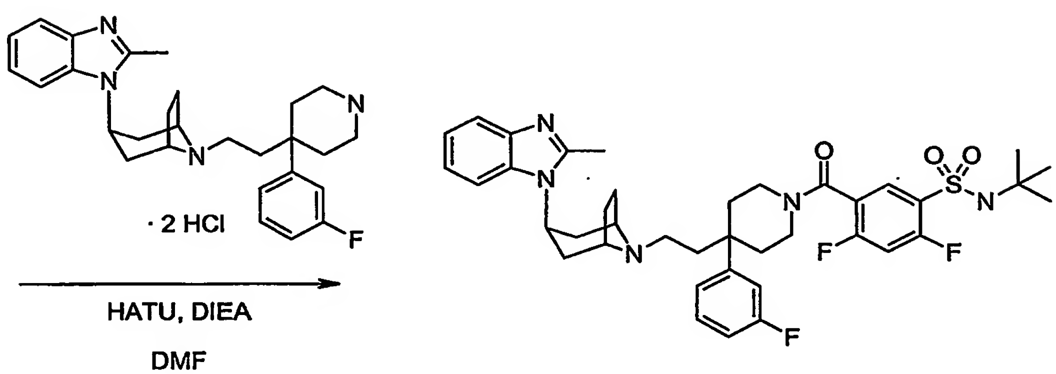
N-(1,1-dimethylethyl)-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide



Prepared according to figure below.

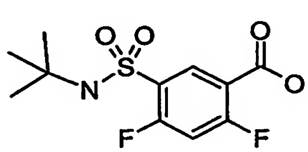
882-3a





Synthesis of 882-3a

5-{[(1,1-dimethylethyl)amino]sulfonyl}-2,4-difluorobenzoic acid



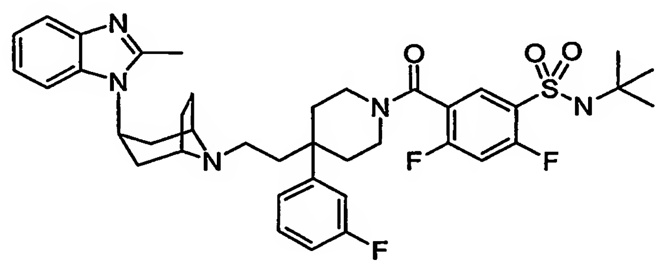
Prepared from a mixture of 5-(chlorosulfonyl)-2,4-difluorobenzoic acid (200 mg, 0.78 mmol, 1 equiv), *tert*-butyl amine (98 µL, 0.94 mmol, 1.2 equiv) and DIEA (280 µL, 1.56 mmol, 2 equiv) following the general procedure for 2,6-

dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 292.3 (M-H)

Synthesis of 882

N-(1,1-dimethylethyl)-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide



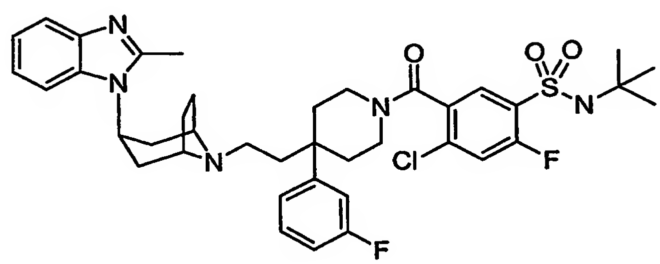
Prepared from a mixture of 5-{[(1,1-dimethylethyl)amino]sulfonyl}-2,4-difluorobenzoic acid 882-3b 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (100mg, 0.16 mmol, 1 equiv), DIEA (117 μL, 0.66 mmol, 4 equiv) and HATU (62 mg, 0.16 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide 1. The crude product was purified by column chromatography on silica gel eluting with 10% 2M NH_3 in methanol in ethyl acetate to afford N-(1,1-dimethylethyl)-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide (example 882) as a white solid (46 mg, 40% yield).

^{1}HNMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.66 (m, 1H), 7.93-6.95 (m, 9H), 4.86 (m, 1H), 4.62 (m, 1H), 4.15 (m, 2H), 3.44-3.14 (m, 5H), 2.92 (m, 3H),

2.58-1.60 (m, 14H), 1.25 (m, 9H). HRMS *m/z* (M+H): Calcd for $C_{39}H_{46}F_3N_5O_3S$, 722.34; found 722.3352.

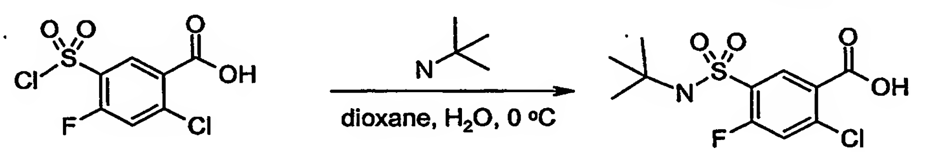
Example 883

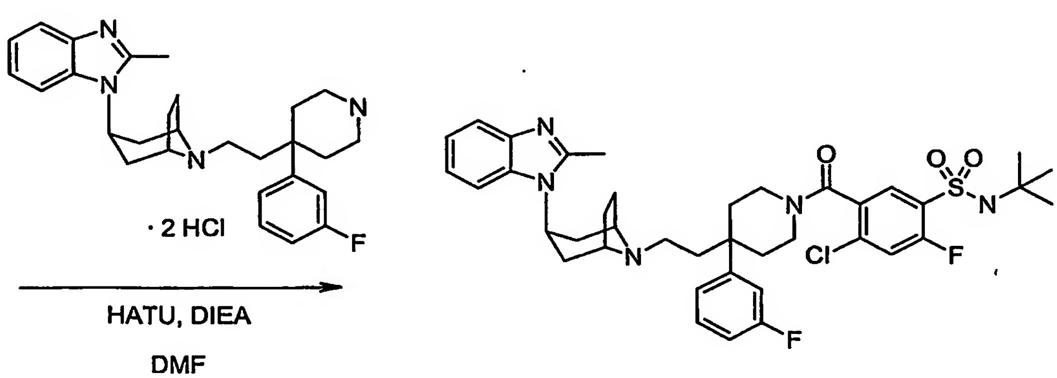
<u>4-chloro-N-(1,1-dimethylethyl)-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide</u>



Prepared according to figure below

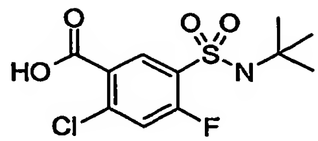
883-4a





Synthesis of 883-4a

2-chloro-5-{[(1,1-dimethylethyl)amino]sulfonyl}-4-fluorobenzoic acid

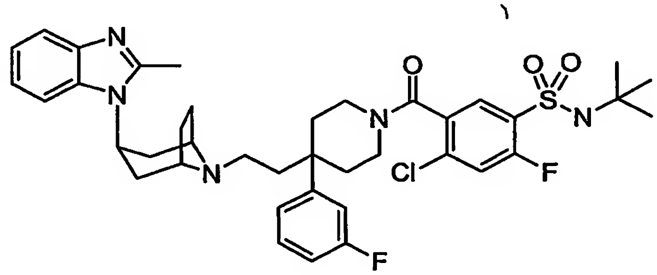


tert-Butyl amine (77 mL, 0.7 mol, 10 equiv) was added to 300 mL dioxane at 0 °C. Ice chips were added to the flask for several minutes before the addition of 2-chloro-5-(chlorosulfonyl)-4-fluorobenzoic acid (20 g, 73.24 mmol, 1 equiv). Both the internal and external temperature of the reaction was maintained at or below 0 °C for 2 h. The reaction was then concentrated half-way and acidified to pH 2 with 1N HCl. The product was extracted into EtOAc. The organics were dried over Na_2SO_4, filtered and concentrated down to give 2-chloro-5-{[(1,1-dimethylethyl)amino]sulfonyl}-4-fluorobenzoic acid 883-4a as a brown solid (21 g; 92% yield).

^{1}H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 7.8 Hz, 1H), 8.06 (broad s, 1H), 7.82 (d, *J* = 9.8 Hz, 1H). ES-LCMS m/z 308.2 (M-H)

Synthesis of 883

4-chloro-N-(1,1-dimethylethyl)-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide



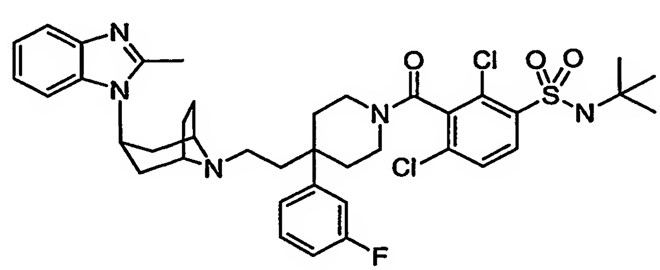
To a solution of 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (32.0 g, 61.6 mmol, 1 equiv) in dimethylformamide (300 mL) was added 2-chloro-5-{[(1,1-dimethylethyl)amino]sulfonyl}-4-fluorobenzoic acid 883-4b (21 g, 67.8 mmol, 1.1 equiv) and *N,N*-diisopropylethyl amine (44 mL, 0.25 mol, 4 equiv). After

stirring at RT for several min, O-(7-azabenzotriazol-1-yl)-*N N,N', N'*-tetramethyluroniumhexafluorophosphate (23.4 g, 61.6 mmol, 1 equiv) was added and the reaction was stirred for 2 h. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with satd. aq. $NaHCO_3$, H_2O and satd. aq. NaCl, then dried over Na_2SO_4, filtered and concentrated. The residue was taken up in 200 mL MeOH and stirred with Amberjet 4400 OH Basic Ion Exchanger (60 g) for 1 h. The mixture was filtered and concentrated and the residue was purified by silica gel flash column chromatography in 20% 2M NH_3 in MeOH in EtOAc to afford 4-chloro-N-(1,1-dimethylethyl)-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide (example 883) as a white solid (21g; 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.86–7.76 (m, 2H), 7.49 (m, 1H), 7.44–7.35 (m, 2H), 7.23 (m, 2H), 7.15–7.04 (m, 3H), 4.55–4.45 (m, 1H), 3.98–3.86 (m, 1H), 3.42–3.35 (m, 1H), 3.25 (m, 2H), 3.05–2.96 (m, 1H), 2.45 (m, 3H), 2.39–2.32 (m, 2H), 2.23-1.99 (m, 2H), 1.92-1.72 (m, 11H), 1.60 (m, 2H), 1.12 (m, 9H). HRMS *m*/z (M+H) Calcd for $C_{39}H_{46}ClF_2N_5O_3S$, 738.30; Found, 738.30.

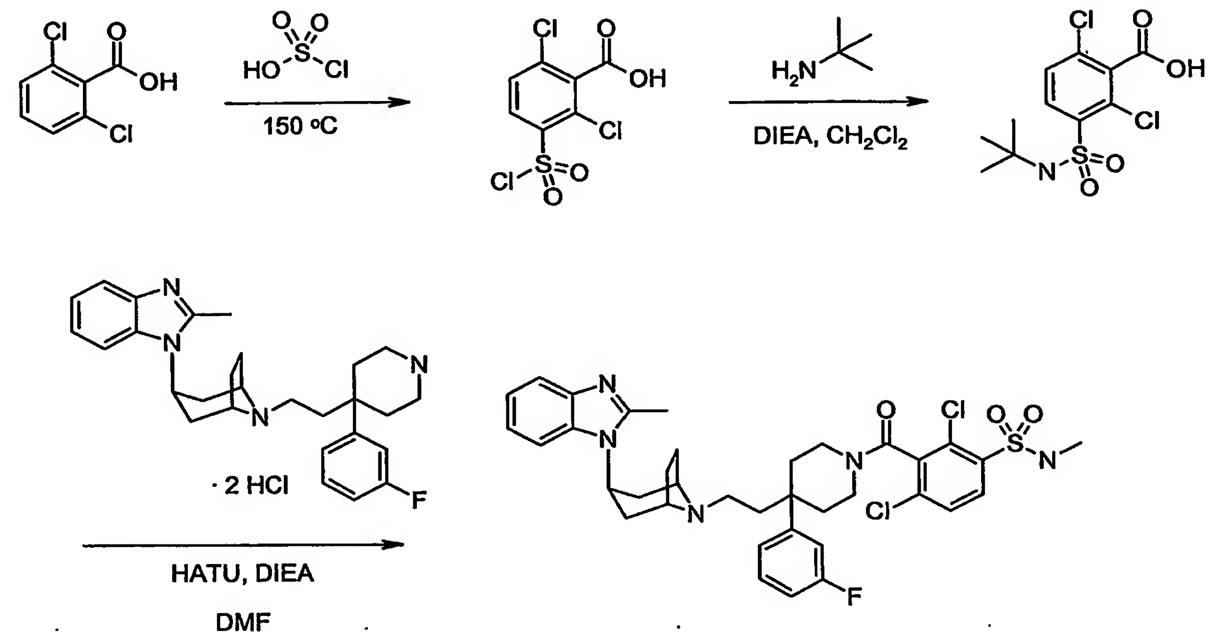
Example 884

2,4-dichloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide



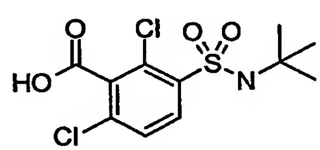
Example 884 was prepared according to figure below.

880-1a 884-5a



Synthesis of 884-5a

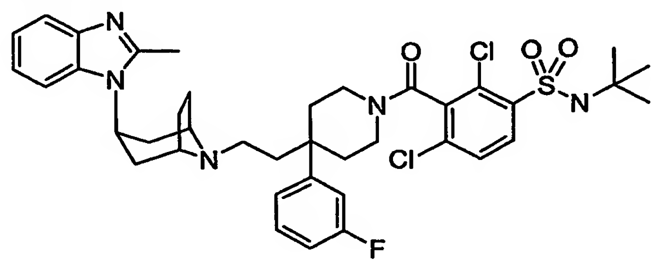
2,6-dichloro-3-{[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid



Prepared from a mixture of 2,6-dichloro-3-{[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid 884-5a (200mg, 0.69 mmol, 1 equiv), *tert*-butyl amine and DIEA (248 µL, 1.38 mmol, equiv) following the general procedure for 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 327.4 (M+H)

Synthesis of 884
2,4-dichloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide

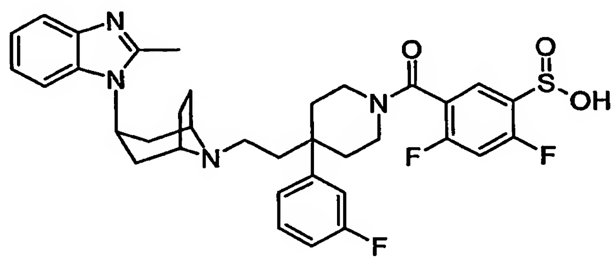


Prepared from a mixture of 2,6-dichloro-3-{[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid 884-5a, 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (100 mg, 0.16 mmol, 1equiv), DIEA (117 µL, 0.66 mmol, 4 equiv) and HATU (62 mg, 0.16 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide (example 880). The crude product was purified by column chromatography on silica gel eluting with 10% 2M NH_3 in methanol in ethyl acetate to afford 2,4-dichloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide 5 as a white solid (21 mg, 17% yield).

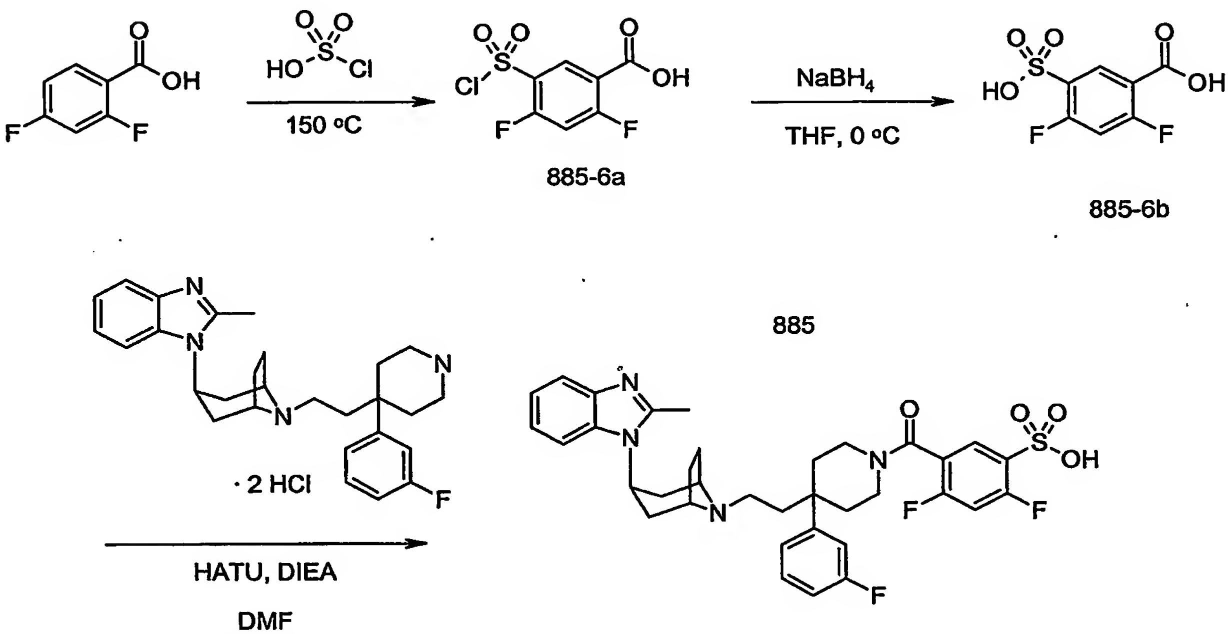
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.66 (m, 1H), 7.47 (m, 1H), 7.39-7.26 (m, 3H), 7.20-6.95 (m, 5H), 4.98 (m, 1H), 4.61 (m, 1H), 4.27 (m, 1H), 3.71 (m, 1H), 3.51 – 3.07 (m, 7H), 2.57 (m, 3H), 2.47-1.37 (m, 11H), 1.23 (m, 9H). HRMS *m/z* (M+H) Calcd for $C_{39}H_{46}Cl_2FN_5O_3S$, 754.2761: Found, 754.2761.

Example 885

2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfinic acid

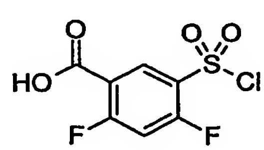


Example was prepared according the figure below.



Synthesis of 885-6a

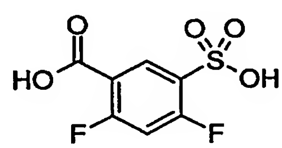
5-(chlorosulfonyl)-2,4-difluorobenzoic acid



A mixture of chlorosulfonic acid (200 mL) and 2,4-difluorobenzoic acid (40 g, 253 mmol, 1 equiv) was heated to 155 °C for 3 h. The reaction was cooled to RT and poured slowly over ice. The product was extracted into ether and the organics dried over $MgSO_4$, filtered and concentrated to give 5-(chlorosulfonyl)-2,4-difluorobenzoic acid **6a** as brown solid (61 g, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (broad s, 1H), 8.72 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 9.5 Hz, 1H). ES-LCMS m/z 255.3 (M-H)

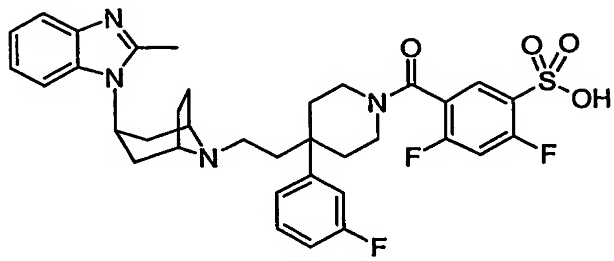
Synthesis of 885-6b
2,4-difluoro-5-sulfobenzoic acid



Sodium borohydride (0.59 g, 15.6 mmol, 8 equiv) was added portionwise to a solution of 5-(chlorosulfonyl)-2,4-difluorobenzoic acid 885-6a (0.5 g, 1.9 mmol, 1 equiv) in 10 mL THF at 0 °C. The reaction was stirred at this temperature for 1 h and then concentrated down and the residue acidified to pH 2 with 5N HCl. The precipitate was removed by filtration and the liquid concentrated down to provide 2,4-difluoro-5-sulfobenzoic acid 885-6b as a white solid (433 mg, 100% yield)

^{1}H NMR (400 MHz, DMSO) δ 8.18 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 10.2 Hz, 1H).

Synthesis of example 885
2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonic acid



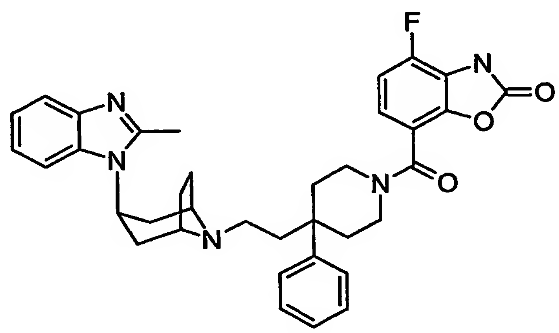
Prepared from a mixture of 2,4-difluoro-5-sulfobenzoic acid 885-6b(580 mg, 0.58 mmol, 2 equiv), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 0.29 mmol, 1 equiv), DIEA (260 μL, 1.45 mmol, 5 equiv) and HATU (110 mg, 0.29 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamid, example 880. The crude product was purified by prep HPLC (HPLC Method C) to afford 2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonic acid (example 885) as a white solid (40 mg, 22% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 1H), 7.53 (m, 1H), 7.47-7.40 (m, 2H), 7.27-7.03 (m, 6H), 4.88 (m, 1H), 3.88-3.05 (m, 4H), 2.64-2.34 (m, 14H, 2.22-1.80 (m, 8H). ES-LCMS m/z 651.3 (M+H).

HPLC Method C

Preparative High Pressure Liquid Chromatography data was acquired using a Waters LC-UV system. The system operates using a Waters Symmetry Shield RP18 3.9x150mm, 5μm column at 35mL/minute. The mobile phase consists of Water (0.1%NH4OH) and MeOH. The gradient used starts a 0% MeOH: 90% Water (0.1%NH4OH) and moves to 90% MeOh : 10% Water (0.1%NH4OH) over 7 minutes. There is a one minute wash of the column using 100% MeOH for one minute, until eight minutes and then original conditions return at 8.1 minutes to 8.5

Example 886
4-fluoro-7-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzoxazol-2(3H)-one

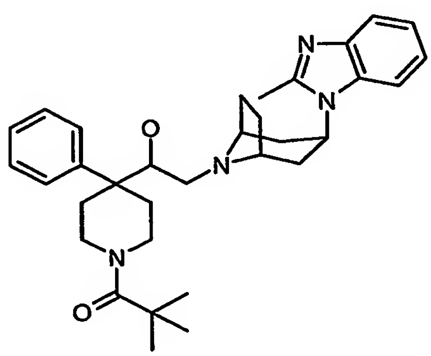


Prepared from a mixture of 4-fluoro-2-oxo-2,3-dihydro-1,3-benzoxazole-7-carboxylic acid (9.8 mg, 0.05 mmol, 1 equiv), endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride (25 mg, 0.05 mmol, 1 equiv), DIEA (36 µL, 0.2 mmol, 4 equiv) and HATU (19 mg, 0.05 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide (example 880). The crude product was purified by prep HPLC (HPLC Method C) to provide 4-fluoro-7-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzoxazol-2(3H)-one as a white solid (5 mg, 17% yield).

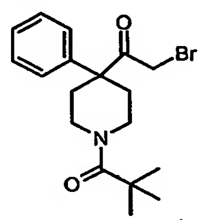
NMR (400 MHz, $CDCl_3$) δ 7.51-7.34 (m, 1H), 7.26-7.22 (m, 1H), 7.16-7.07 (m, 4H), 4.53 (m, 1H), 3.94 (m, 1H), 3.5-3.1 (m, 6H), 2.54-2.05 (m, 12H), 1.96-1.59 (m, 6H). ES-LCMS *m/z* 608.17 (M+H).

Example 887

1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]-2-[3-(2-methyl-1 *H*-benzimidaol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanol



Synthesis of 2-bromo-1-[1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]ethanone

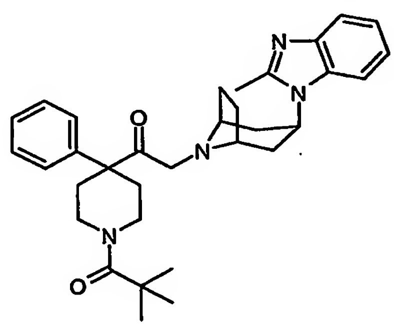


To a suspension of 4-acetyl-4-phenyl piperdine hydrochloride (20.8mmol) in DCM (200ml) was added TEA (541.1mmol) and the mixture was stirred under an inert atmosphere for 10 minutes. Pivaloyl chloride (22.8mmol) was added and the mixture was stirred until HPLC analysis indicated that the reaction was complete. Water and EtOAc were added. The ethyl acetate layer was separated and washed with satd. $NaHCO_3$, water, brine and dried (Na_2SO_4). Removal of solvent under vacuum gave the intermediate ketone, which was used directly in the next step. ^{1}H NMR (400 MHz, DMSO d-6) 7.21-7.40 (m, 5 H), 3.77-3.82 (dt, 2 H), 3.14-3.21 (t, 2 H), 2.45-2.51 (m, 2H), 2.31-2.41 (d, 2H), 1.20 (s, 2H), 1.14 (s, 9H). LCMS *m/z* (M+H) calcd: 287.48 obsd: 288.44.

To a solution of 1-[1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]ethanone in MeOH (125ml) at 0° C. Br_2 was added (24.5mmol) dropwise over 10 minutes. The mixture was stirred 12 hrs. at room temperature under an inert atmosphere. H_2O (20ml) was added and the resulting mixture was stirred for

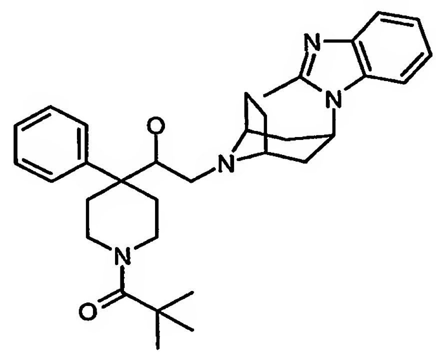
an additional 0.5 hr. Et_2O and water (250ml 1:1) were added, the organic layer was washed with water, satd. K_2CO_3 solution, dried (Na_2SO_4) and the solvent was removed *in-vacuo* to give **2** as a lightly colored powder (7g, 92%). HPLC: rt=5.26 min. This compound was used directly in the following step.

The synthesis of 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]-2-[3-(2-methyl-1 *H*-benzimidaol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanone



To the amine IV in scheme III (3mmol) in Et_2O was added TEA (17.9mmol) and the reaction mixture was stirred under inert atmosphere for 1hr. Next, 2-bromo-1-[1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]ethanone (2.7mmol) in Et_2O (20ml) was added and the resulting mixture was stirred overnight. Benzene (50ml) and TEA (14.3mmol) were added to the reaction and the whole was heated to 90^0 C overnight. The reaction was cooled to room temperature and concentrated *in-vacuo*. The crude material in DCM was washed with brine, and water and then dried (Na_2SO_4). Concentration under vacuum gave 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]-2-[3-(2-methyl-1 *H*-benzimidaol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanone, which was purified by silica gel chromatoghraphy (DCM: MeOH; 9.5: 0.5) to give (400mg, 30%) as a white powder. ^1H NMR (400 MHz, CDCl3), 7.67 (d,1H), 7.29-7.42 (m, 6H), 7.08-7.22 (m, 2H), 4.63-4.78 (m, 1H), 4.08-4.18 (m, 3H), 3.28-3.39 (m, 2H), 3.12-3.23 (m, 2H), 3.08-3.10 (s, 2H), 2.61 (s, 3H), 2.50(m, 2H), 2.39-2.40 (m, 2H), 2.10 (s, 2H), 1.84-1.90 (m, 2H), 1.61 (s, 3H), 1.28 (s, 9H). LCMS *m/z* (M+H) calcd: 526.72, obsd: 527.45

The syntheis of 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]-2-[3-(2-methyl-1 *H*-benzimidaol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanol

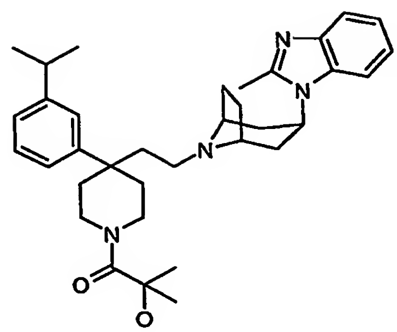


To a solution of 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperdin-4-yl]-2-[3-(2-methyl-1 *H*-benzimidaol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanone (30mg) in MeOH (5ml) was added $NaBH_4$ (0.9mmol) and the reaction mixture was stirred overnight. Satd. $NaHCO_3$ was added and the product was extracted with DCM (3x). The organics were dried (Na_2SO_4). Removal of solvent under of vacuum gave the desired product 4 as a white solid. ^{1}H NMR ($CDCl_3$) 7.64-7.70 (m, 1H), 7.35-7.41 (m, 4H), 7.29-7.30 (m, 1H), 7.11 (m, 2H), 4.49-4.62 (m, 1H), 4.22-4.30 (s, 2H), 3.50-3.60 (dd, 1H), 3.34 (t, 1H), 3.15 (t, 1H), 2.90-2.77 (q, 2H), 2.51 (s, 3H), 2.34-2.44 (m, 3H), 2.22 (d, 1H), 2.1 (dd, 1H), 1.94 (m, 4H), 1.90 (m,1H), 1.71-1.80 (m, 3H), 1.25 (s, 9H). HPLC (3.483 min, 100%)

HPLC : ZORBAX (2.1x50mm; 3.5micron), T=40°C; ACN/water+0.05%TFA; 0-to-95% over 8min.

Example 888

3-(4-(3-isopropylphenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazole-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperdin-1-yl)2,2-dimethyl-3-oxopropan-1-ol

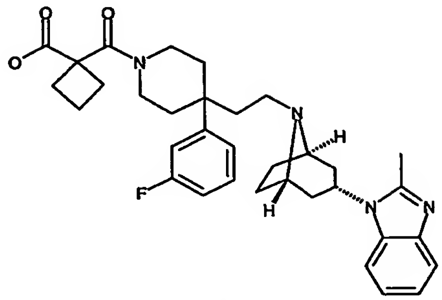


This compound was prepared from 3-isopropyl phenylmagnesium bromide and 16a according to the procedure described in example 16. To a solution of 3-hydroxy-2,2-dimethylpropanoic acid (0.14mmol), DIEA (1.7mmol) and HATU (0.14mmol) in DMF was added 1-(8-{2-[4(-3-isopropylphenyl)piperdin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole hydrochloride (0.13mmol) in the same solvent and stirring was continued overnight. The reaction mixture was diluted with EtOAc, and washed with $NaHCO_3$, water, and satd. brine and dried (Na_2SO_4). The solvent was removed *in-vacuo* and the crude material was purified by HPLC to 1 as a clear film. H NMR (400MHz, CDCl3) 9.72 (s, 2H), 8.48 (s, 1H), 7.64 (d, 1H), 7.04-7.36 (m, 8H), 4.74 (t, 1H), 3.19-3.32 (m, 4H), 2.88-2.97 (m, 3H), 2.60 (s, 3H), 2.43-2.47 (d, 4H), 2.37 (s,2H), 1.86-2.33 (m, 10H), 1.77 (d, 2H), 1.26-1.28 (d, 6H). LCMS *m/z* (M+H) calc: 556.79, obsd: 557.79.

Example 889

Preparation of

1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-cyclobutanecarboxylic acid

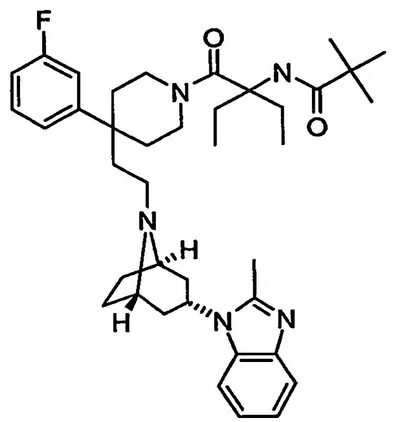


1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-cyclobutanecarboxylic acid was obtained from a solution of 1-(ethoxycarbonyl)cyclobutane carboxylic acid (0.031 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5 to produce 1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-cyclobutanecarboxylic acid ethyl ester. The ester (0.100 g, 0.167 mmol), 5 N NaOH (10 ml) and ethanol (4 ml) was stirred at 90°C for 3 hrs. The reaction was evaporated to dryness and residue was suspend in water (10 ml) and neutralized with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was dried using magnesium sulfate and concentrated down to form the title compound as a white solid (0.078 g, 81%). 1H NMR (400 MHz, CDCl3), 7.70 (m,1H), 7.32-7.16 (m, 4H), 7.04 (m, 1H), 6.97-6.92 (m, 2H), 4.74 (m, 1H), 4.24-3.99 (m, 4H), 3.44-3.40 (m, 1H), 3.30 (br, 2H), 3.19 (m, 1H), 3.10 (m, 1H), 2.77 (m, 1H), 2.59 (s, 3H), 2.44-2.28 (br, 4H) 2.10-2.00 (m, 4H), 1.91-1.78 (m, 8H), 1.66 (m, 2H). ES-LCMS *m/z* 573 (M+1).

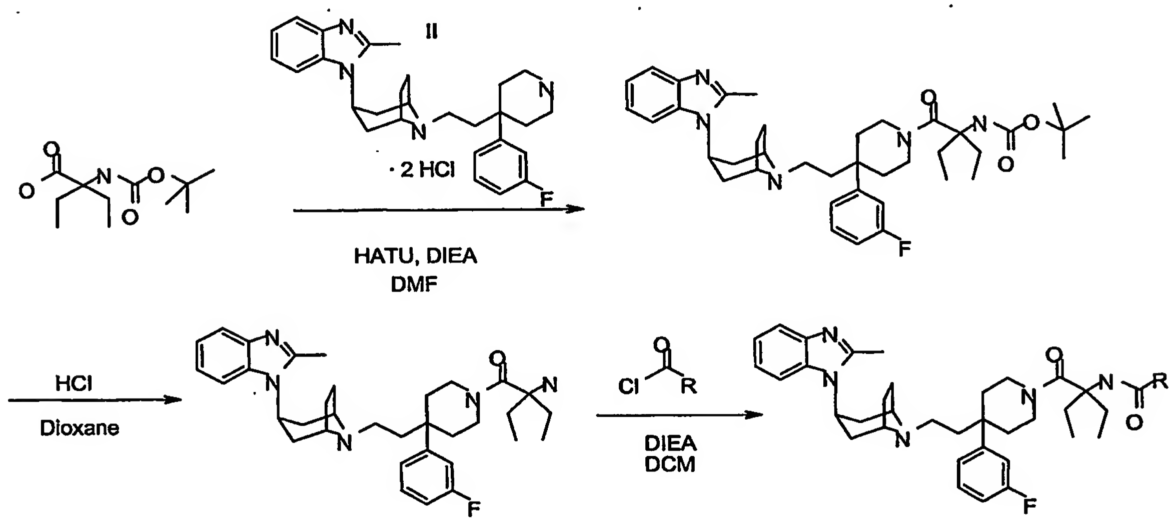
Example 890

Preparation of

N-[1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide

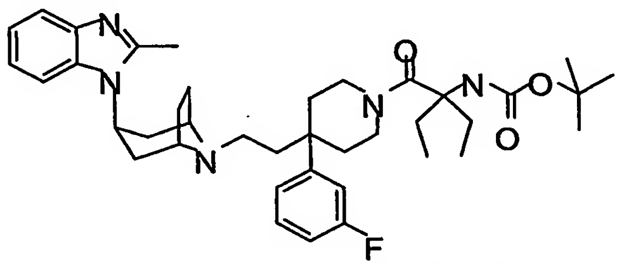


Prepared as outlined below.



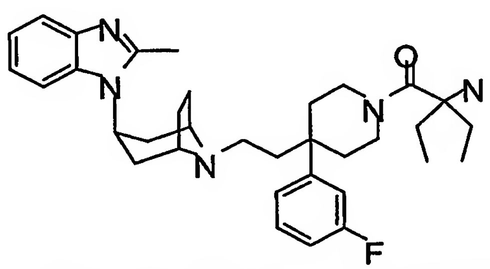
Example 890: R = t-butyl
Example 891: R = methyl

Preparation of [1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester



A mixture of 2-tert-Butoxycarbonylamino-2-ethyl-butyric acid (0.291 g, 1.35 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.700 g, 1.35 mmol), and HATU (0.514 g, 1.35 mmol) following the procedure outlined in example 5. Obtained 0.712 g (80%) of an oil. ES-LCMS *m/z* 660(M+1).

Preparation of 2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one



[1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester was treated with 4N HCl (20ml) in dioxane and then solvent was removed in vacuo. Residue was dissloved in water nuetralized and extracted with EtOAcX3 to yield 0.600 g (99%) of the deprotected amine product as an oil. ES-LCMS *m/z* 560(M+1).

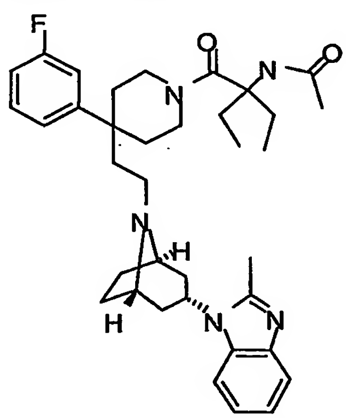
Preparation of title example 890:

A solution of 2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-

1-one (0.100 g, 0.178 mmol), 2,2-Dimethyl-propionyl chloride (0.021 g, 0.178 mmol)and DIEA (0.069 g, 0.534 mmol) were stirred at room temperature in DCE (3 ml) for 2 hours. Solvent was removed and compound was purified by RP-HPLC to yield 0.065 g (57%). 1H NMR (400 MHz, CDCl3) 7.82 (s, 1H), 7.67 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.16 (m, 2H), 7.09 (m, 1H), 6.99 (m, 1H), 4.60 (m, 1H), 4.07 (br, 2H), 3.32-3.23 (m, 4H), 2.79 (m, 2H), 2.57 (s, 3H), 2.36 (m, 2H), 2.21 (m, 2H), 1.92 (m, 6H), 1.80 (m, 4H), 1.65 (m, 6H), 1.23 (s, 9H) 0.76 (br, 5H). ES-LCMS *m/z* 644(M+1).

Example 891

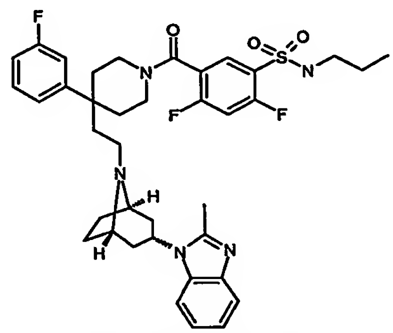
Preparation of N-[1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide



A solution of 2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.100 g, 0.178 mmol), acetyl chloride (0.014 g, 0.178 mmol)and DIEA (0.069 g, 0.534 mmol) were stirred at room temperature in DCM (3 ml) for 2 hours. Solvent was removed and compound was purified by RP-HPLC to yield 0.072 g (67%). 1H NMR (400 MHz, CDCl3) 7.67 (m, 1H), 7.40-7.29 (m, 2H), 7.18 (m, 2H), 7.09 (m, 1H), 6.99 (m, 2H), 4.60 (m, 1H) 4.04 (br, 2H), 3.32-3.23 (m, 4H), 2.74 (m, 2H), 2.57(s, 3H), 2.36 (m, 2H), 2.20 (m, 2H), 2.01 (s, 3H), 1.92 (m, 6H), 1.82-1.63 9 (m, 10H), 0.78 (br, 5H). ES-LCMS *m/z* 602(M+1).

Example 892

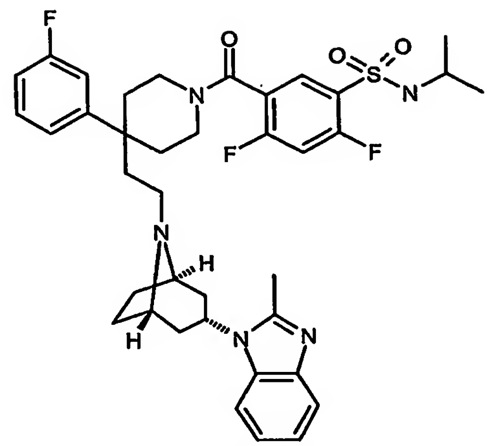
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-propyl-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-propyl-benzenesulfonamide (0.068 g, 53%) was obtained from a solution of 2,4-Difluoro-5-propylsulfamoyl-benzoic acid (ACID 34) (0.050 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. 1H NMR (400MHz, CDCl3)7.63 (m, 1H), 7.36-7.28 (m, 3H), 7.15 (m, 2H), 7.08 (m, 1H), 6.96 (m, 3H), 4.60 (m, 1H), 4.22 (m, 1H), 3.37 (m, 2H), 3.23 (m, 3H), 2.98 (m, 2H) 2.56 (s, 3H), 2.38 (m, 3H), 2.12 (m, 1H), 1.93- 1.82 (m, 11H), 1.62 (m, 2H), 1.51 (m, 2H), 0.89 (m, 3H). ES-LCMS *m/z* 708(M+1).

Example 893

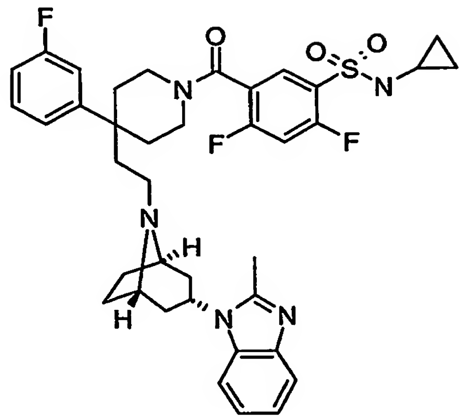
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-isopropyl-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-isopropyl-benzenesulfonamide (0.071 g, 55%) was obtained from a solution of 2,4-Difluoro-5-isopropylsulfamoyl-benzoic acid (ACID 35) (0.050 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. 1H NMR (400MHz, CDCl3)7.96 (m, 1H), 7.66 (m, 1H), 7.36-7.29 (m, 2H), 7.17 (m, 2H), 7.08 (m, 1H), 6.98 (m, 3H), 4.91 (m, 1H), 4.61 (m, 1H), 4.23 (m, 1H), 3.54 (m, 1H), 3.37 (m, 1H), 3.25 (m, 3H), 2.56 (s, 3H), 2.41-2.28 (m, 3H), 2.14 (m, 1H), 1.96-1.74 (m, 10H), 1.63 (m, 2H), 1.12 (m, 6H). ES-LCMS *m/z* 708(M+1).

Example 894

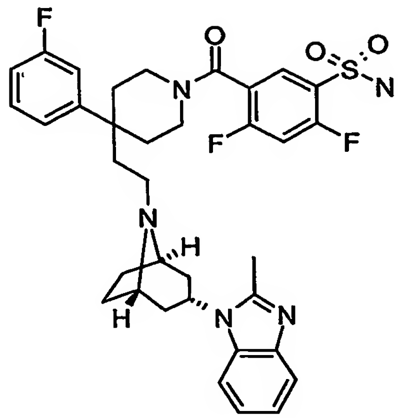
Preparation of N-Cyclopropyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide



N-Cyclopropyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide (0.081 g, 64%) was obtained from a solution of 5-Cyclopropylsulfamoyl-2,4-difluoro-benzoic acid (ACID 36) (0.050 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. 1H NMR (400MHz, CDCl3)8.01 (m, 1H), 7.66 (m, 1H), 7.37-7.29 (m, 2H), 7.16 (m, 2H), 7.08-6.90 (m, 4H), 5.47 (m, 1H), 4.64 (m, 1H), 4.24 (m, 1H), 3.37 (m, 2H), 3.27-3.17 (m, 3H), 2.57 (s, 3H), 2.42-2.29 (m, 4H), 2.13 (m, 1H), 1.94-1.78 (m, 10 H), 1.65 (m, 2H), 0.65 (m, 4H). ES-LCMS *m/z* 706(M+1).

Example 895

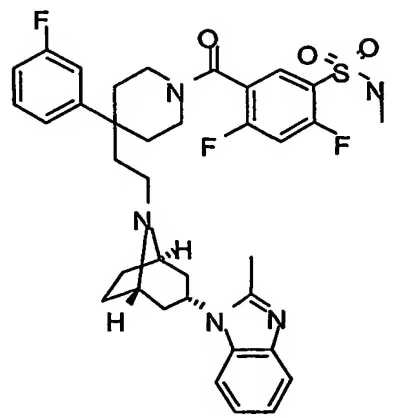
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide (0.059 g, 49%) was obtained from a solution of 2,4-Difluoro-5-sulfamoyl-benzoic acid (ACID 31) (0.043 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo [3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. 1H NMR (400MHz, CDCl3) 7.98 (m, 1H), 7.66 (m, 1H), 7.37-7.29 (m, 2H), 7.18-6.97 (m, 6H), 5.35 (m, 1H), 4.61 (m, 1H), 4.20 (m, 1H), 3.38 (m, 2H), 3.25 (m, 3H), 2.56 (s, 3H), 2.44-2.27 (m, 3H), 2.14 (m, 1H), 1.96-1.79 (m, 10 H), 1.66 (m, 2H). ES-LCMS *m/z* 666(M+1).

Example 896

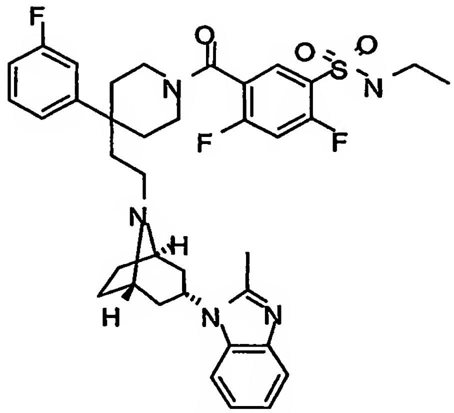
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-methyl-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-methyl-benzenesulfonamide (0.063 g, 51%) was obtained from a solution of 2,4-Difluoro-5-methylsulfamoyl-benzoic acid (ACID 32) (0.045 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. 1H NMR (400MHz, CDCl3) 7.98 (m, 1H), 7.68 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.19 (m, 2H), 7.09 (m, 1H), 6.99 (m, 3H), 4.82 (m, 1H), 4.63 (m, 1H), 4.23 (m, 1H), 3.39 (m, 2 H), 3.30 (m, 2H), 3.22 (m, 1H), 2.74 (s, 3H), 2.59 (s, 3H), 2.42 (m, 2H), 2.29 (m, 2H), 2.17 (m, 2H), 1.98-1.71 (m, 10H), 1.67 (m, 2H). ES-LCMS *m/z* 680(M+1).

Example 897

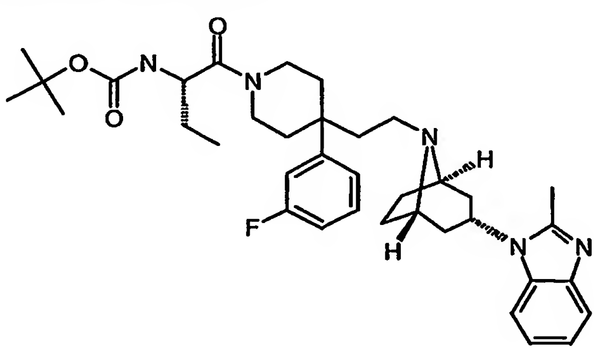
Preparation of N-Ethyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide



Preparation of N-Ethyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide (0.067 g, 54%) was obtained from a solution of 5-Ethylsulfamoyl-2,4-difluoro-benzoic acid (ACID 33) (0.047 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. 1H NMR (400MHz, CDCl3) 7.98 (m, 1H), 7.68 (m, 1H), 7.39 (m, 1H), 7.31 (m, 1H), 7.18 (m, 2H), 7.09 (m, 1H), 6.98 (m, 3H), 4.81 (br, 2H), 4.20 (m, 1H), 3.38 (m, 4H), 3.21 (m, 1H), 3.16 (m, 2H), 2.61 (s, 3H), 2.44 (m, 2H), 2.31 (m, 1H), 2.19 (m, 1H), 2.02-1.61 (m, 12H), 1.16 (m, 3H). ES-LCMS *m/z* 694(M+1).

Example 898

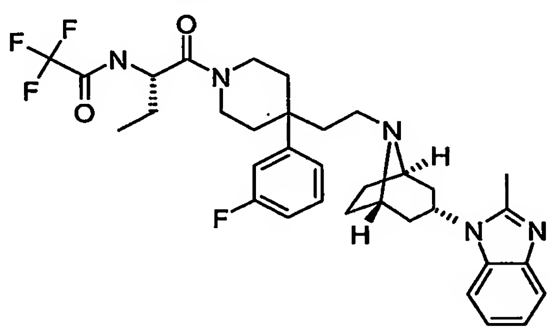
Preparation of [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester



[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 66%) was obtained as an oil from 2-tert-Butoxycarbonylamino-butyric acid (0.298 g, 1.40 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 632(M+1).

Example 899

Preparation of 2,2,2-Trifluoro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide

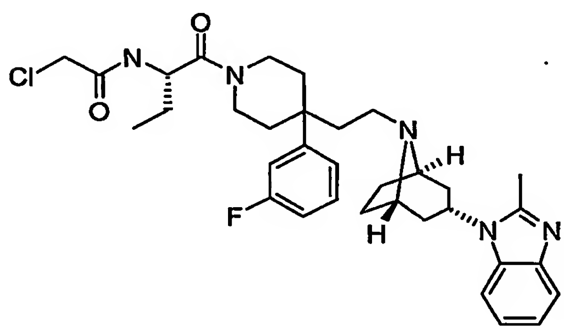


2,2,2-Trifluoro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.049 g, 0.09 mmol, trifluoroaceticanhydirde (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure

outlined in example 890 to give the title compound, 2,2,2-Trifluoro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide(0.034 g, 60%) as an oil. ES-LCMS *m/z* 628(M+1).

Example 900

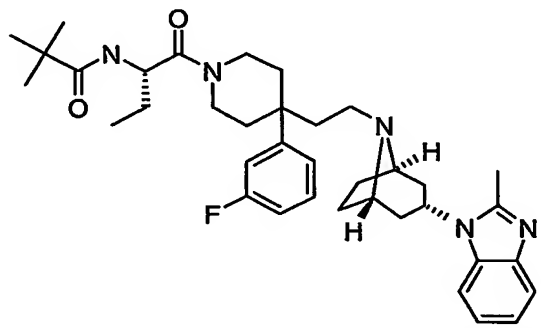
Preparation of 2-Chloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide



2-Chloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.049 g, 0.09 mmol, Chloro-acetyl chloride (0.010 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2-Chloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide (0.024 g, 44%) as an oil. ES-LCMS *m/z* 608(M+1).

Example 901

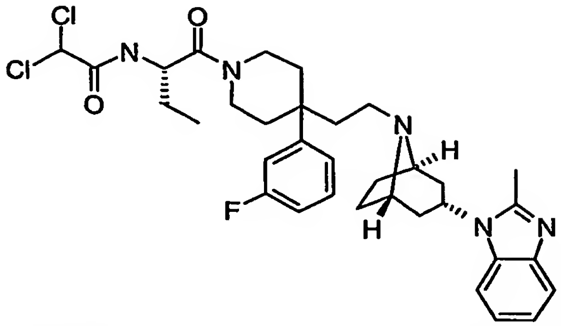
Preparation of N-[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide



N-[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.049 g, 0.09 mmol, 2,2-Dimethyl-propionyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, N-[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide (0.030 g, 54%) as an oil. ES-LCMS *m/z* 616(M+1).

Example 892

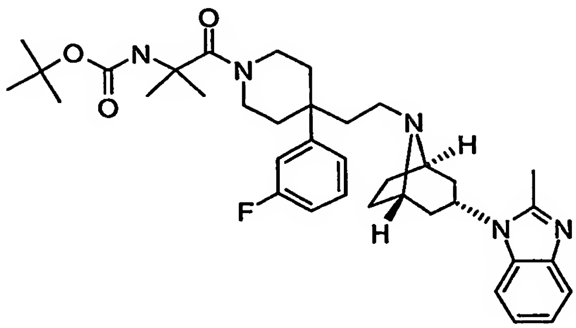
Preparation of 2,2-Dichloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide



2,2-Dichloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.049 g, 0.09 mmol, Dichloro-acetyl chloride(0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2,2-Dichloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide (0.039 g, 67%) as an oil. ES-LCMS *m/z* 642(M+1).

Example 893

Preparation of [2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester

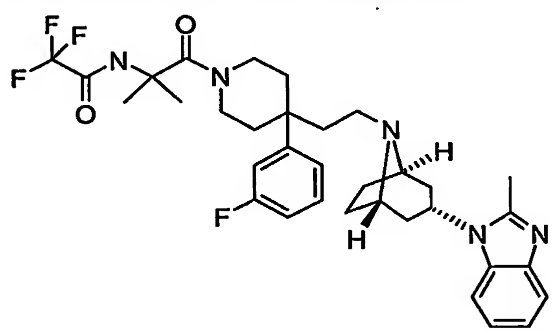


2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester

(0.610 g, 69%) was obtained as a oil from 2-tert-Butoxycarbonylamino-2-methyl-propionic acid (0.284 g, 1.40 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 632(M+1).

Example 904

Preparation of 2,2,2-Trifluoro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide



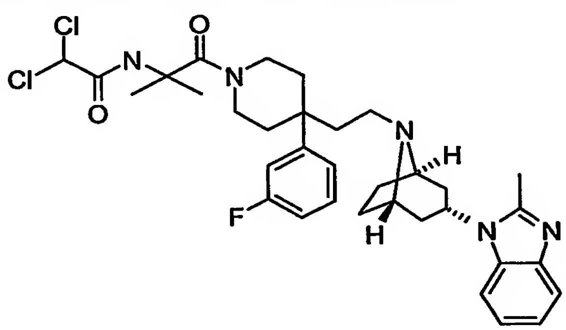
2,2,2-Trifluoro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide

was obtained from treating 2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-

dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester (0.610 g, 0.97 mmol) with HCl as outlined in the procedure in example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one(0.510 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.050 g, 0.09 mmol, trifluoroaceticanhydirde (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2,2,2-Trifluoro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide(0.024 g, 42%) as an oil. ES-LCMS *m/z* 628(M+1).

Example 905

Preparation of 2,2-Dichloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide



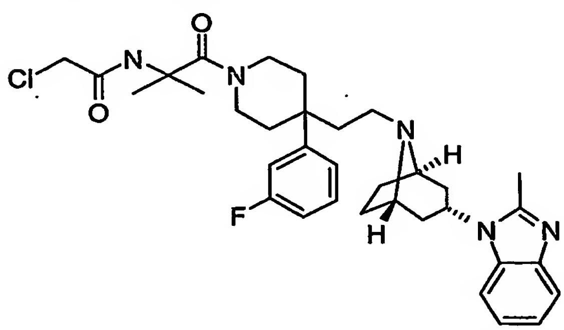
2,2-Dichloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide

was obtained from treating 2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester (0.610 g, 0.97 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-

yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.510 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2,2-Dichloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide(0.028 g, 48%) as an oil. ES-LCMS *m/z* 642(M+1).

Example 906

Preparation of 2-Chloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide

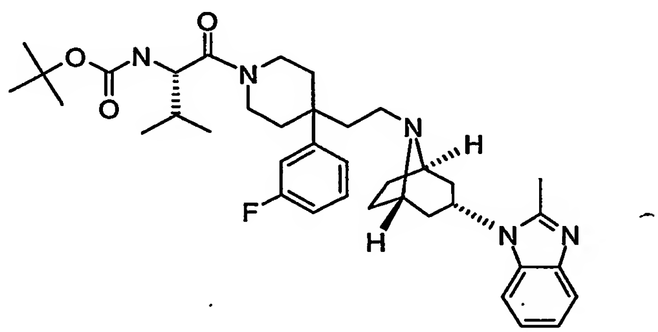


2-Chloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide was obtained from treating 2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester (0.610 g, 0.97 mmol) with HCl as outlined in the procedure for Example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one(0.510 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.050 g, 0.09 mmol, Chloro-acetyl chloride(0.010 g, 0.09 mmol) and DIEA (0.034 g,

0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-Chloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide (0.027 g, 49%) as an oil. ES-LCMS *m/z* 608 (M+1).

Example 907

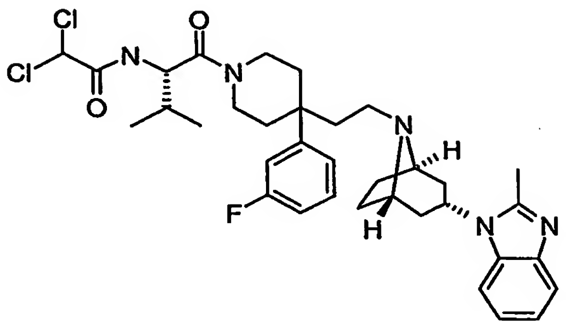
Preparation of 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate



1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate (0.614 g, 68%) was obtained as a oil from *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-L-valine (0.303 g, 1.40 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 648(M+1).

Example 908A

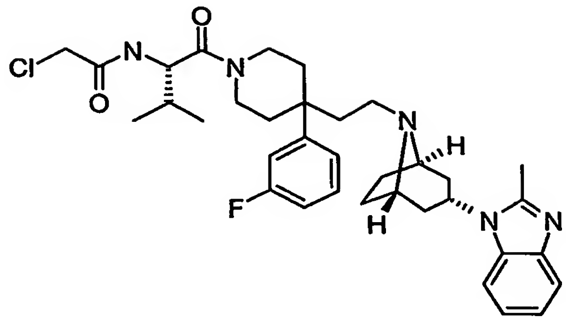
Preparation of 2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide



2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2,1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate(0.614 g,0.95 mmol) with HCl as outlined in the procedure for Example 890 to form {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}amine (0.512 g, 99%). {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl} amine(0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide(0.031 g, 53%) as an oil. ES-LCMS *m/z* 656 (M+1).

Example 908B

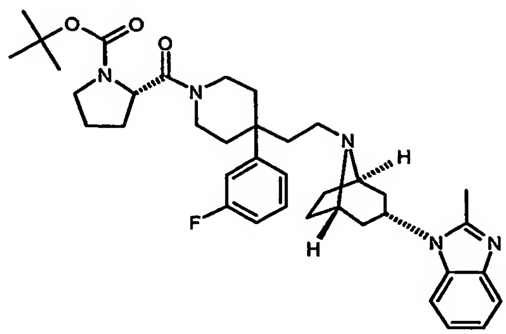
Preparation of 2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide



2-chloro-N-{(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate(0.614 g,0.95 mmol) with HCl as outlined in the procedure for Example 890 to form {(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}amine (0.512 g, 99%). {(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl} amine(0.050 g, 0.09 mmol), Chloro-acetyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-chloro-N-{(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide(0.037 g, 66%) as an oil. ES-LCMS m/z 622 (M+1).

<u>Example 909</u>

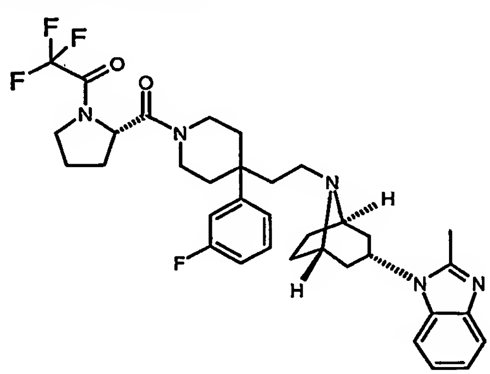
<u>Preparation of 1,1-dimethylethyl (2*S*)-2-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate</u>



1,1-dimethylethyl (2*S*)-2-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate(0.645 g, 72%) was obtained as a oil from 1-{[(1,1-dimethylethyl)oxy]carbonyl}-L-proline(0.301 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 644(M+1).

Example 910

Preparation of 1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[1-(trifluoroacetyl)-L-prolyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole

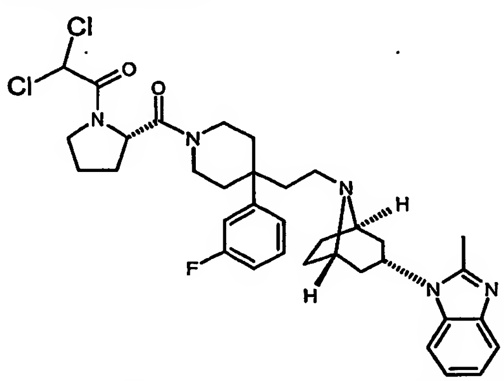


1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[1-(trifluoroacetyl)-L-prolyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole was obtained from treating 1,1-dimethylethyl (2*S*)-2-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate (0.645 g, 1.01 mmol) with HCl

as outlined in the procedure for Example 890 to form 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-L-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole(0.545 g, 99%).1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-L-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole(0.050 g, 0.09 mmol), trifluoroaceticanhydirde (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[1-(trifluoroacetyl)-L-prolyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole(0.021 g, 36%) as an oil. ES-LCMS *m/z* 640 (M+1).

Example 911

Preparation of 1-((1*R*,5*S*)-8-{2-[1-[1-(dichloroacetyl)-L-prolyl]-4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

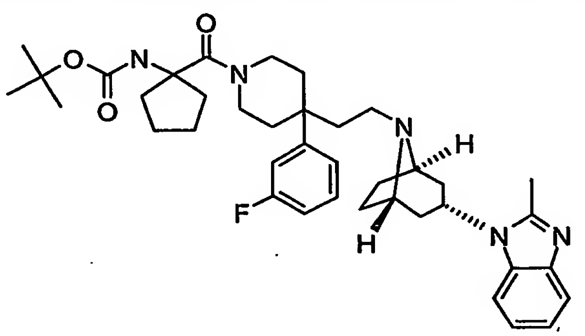


1-((1*R*,5*S*)-8-{2-[1-[1-(dichloroacetyl)-L-prolyl]-4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole was obtained from treating 1,1-dimethylethyl (2*S*)-2-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate (0.645 g, 1.01 mmol) with HCl as outlined in the procedure for Example 890 to form 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-L-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole(0.545 g, 99%).1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-L-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-

benzimidazole(0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol)and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 1-((1*R*,5*S*)-8-{2-[1-[1-(dichloroacetyl)-L-prolyl]-4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (0.029 g, 49%) as an oil. ES-LCMS *m/z* 654 (M+1).

Example 912

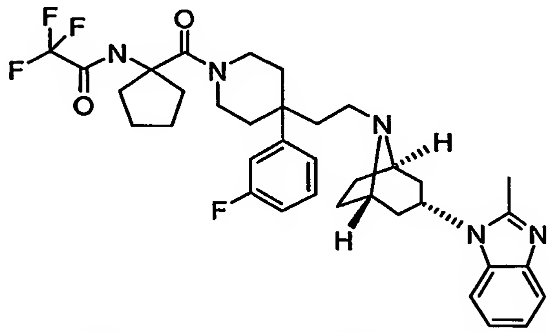
Preparation of 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}carbamate



1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}carbamate (0.627 g, 68%) was obtained as a oil from 1-({[(1,1 dimethylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic acid (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 658(M+1).

Example 913

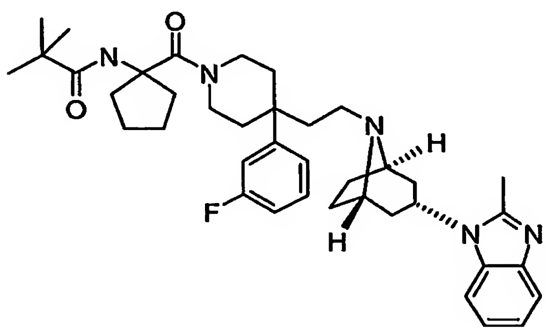
Preparation of 2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}acetamide



2,2,2-trifluoro-N-{1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}carbamate(0.627 g, 0.95 mmol) with HCl as outlined in the procedure for Example 890 to form 1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine(0.528 g, 99%). 1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine(0.050 g, 0.09 mmol), trifluoroacetic anhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2,2-trifluoro-N-{1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}acetamide (0.027 g, 46%) as an oil. ES-LCMS m/z 654 (M+1).

Example 914

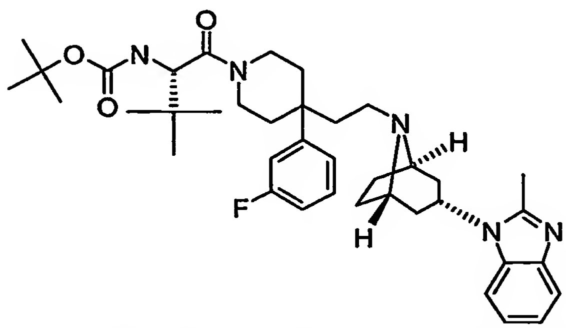
Preparation of *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}-2,2-dimethylpropanamide



N-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}-2,2-dimethylpropanamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}carbamate (0.627 g, 0.95 mmol) with HCl as outlined in the procedure for Example 890 to form 1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine(0.528 g, 99%). 1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine(0.050 g, 0.09 mmol), 2,2-Dimethyl-propionyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}-2,2-dimethylpropanamide (0.031 g, 54%) as an oil. ES-LCMS *m/z* 642 (M+1).

Example 915

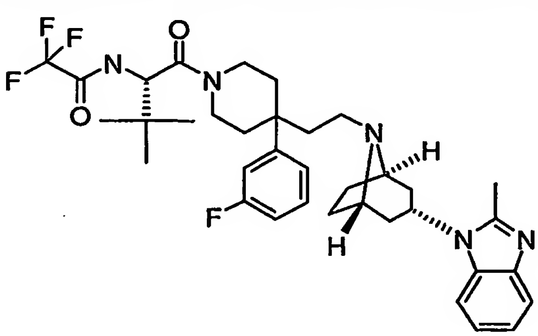
Preparation of 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}carbamate



1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}carbamate(0.591 g, 64%) was obtained as a oil from *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-methyl-L-valine (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 660(M+1).

Example 916

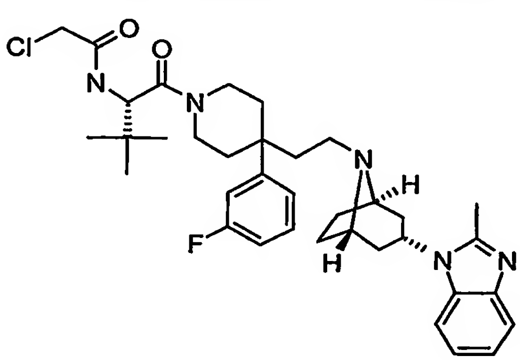
Preparation of 2,2,2-trifluoro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2,2-dimethylpropyl}acetamide



2,2,2-trifluoro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine(0.500 g, 99%). 2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), trifluoroaceticanhydirde (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2,2-trifluoro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide(0.033 g, 56%) as an oil. ES-LCMS *m/z* 656 (M+1).

Example 917

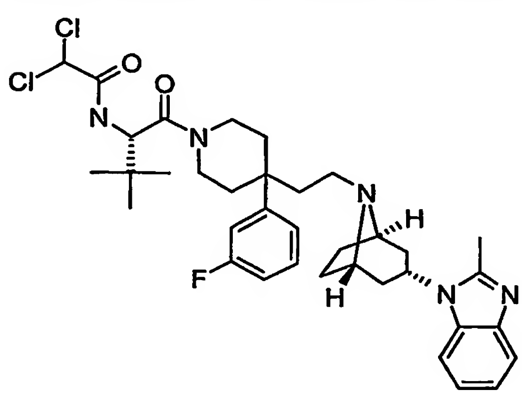
Preparation of 2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide



2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine(0.500 g, 99%). 2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), Chloro-acetyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide (0.038 g, 66%) as an oil. ES-LCMS *m/z* 636 (M+1).

Example 918

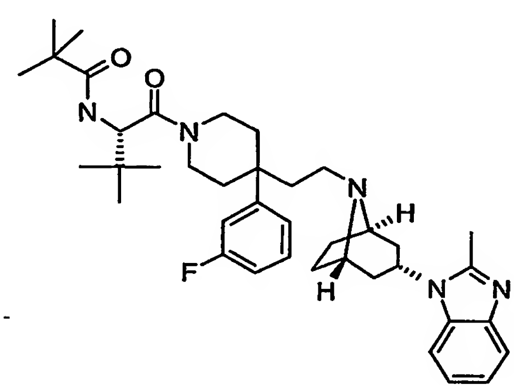
Preparation of 2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide



2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate, example 915, (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine(0.500 g, 99%). 2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol)and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2,2-dimethylpropyl}acetamide(0.036 g, 60%) as an oil. ES-LCMS *m/z* 670 (M+1).

Example 919

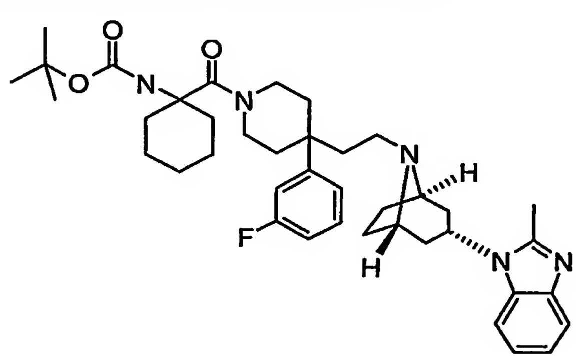
Preparation of *N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}-2,2-dimethylpropanamide



N-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}-2,2-dimethylpropanamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate, example 915, (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine(0.500 g, 99%). 2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), 2,2-Dimethyl-propionyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, *N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}-2,2-dimethylpropanamide(0.032 g, 55%) as an oil. ES-LCMS *m/z* 644 (M+1).

Example 920

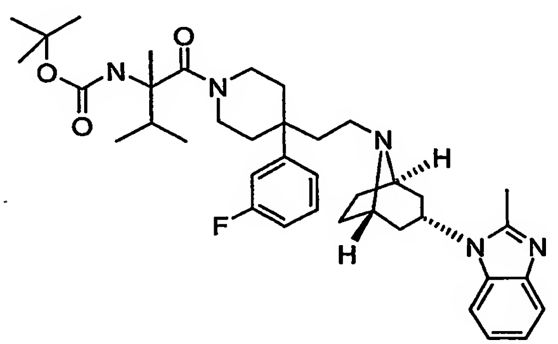
Preparation of 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]cyclohexyl}carbamate



1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]cyclohexyl}carbamate (0.598 g, 64%) was obtained as a oil from 1-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 672(M+1).

Example 921

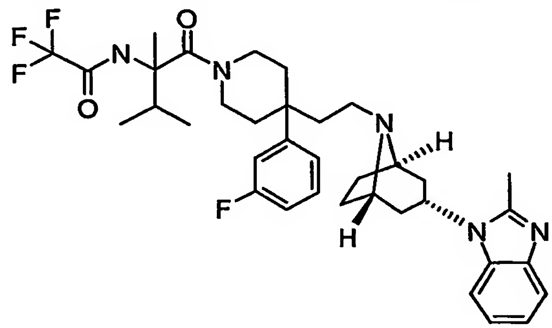
Preparation of 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate



1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} carbamate (0.623 g, 67%)was obtained as a oil from *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-methylisovaline (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 660(M+1).

Example 922

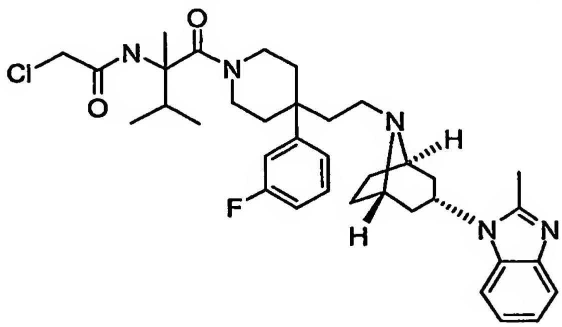
Preparation of 2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide



2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.050 g, 0.09 mmol), trifluoroaceticanhydirde (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} acetamide(0.036 g, 61%) as an oil. ES-LCMS *m/z* 656 (M+1).

Example 923A

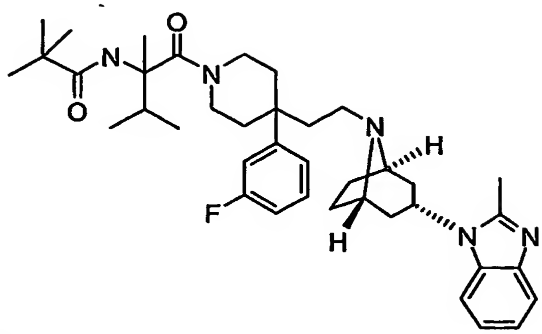
Preparation of 2-chloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide



2-chloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.050 g, 0.09 mmol), Chloro-acetyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-chloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide(0.030 g, 52%) as an oil. ES-LCMS *m/z* 636 (M+1).

Example 923B

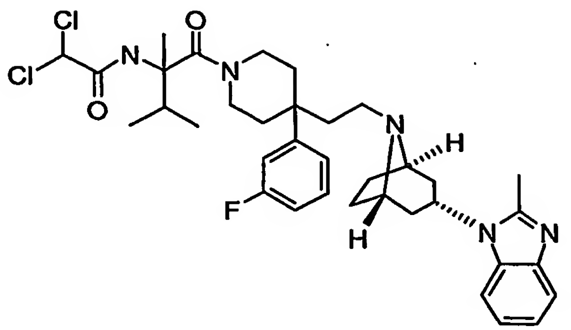
Preparation of *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}-2,2-dimethylpropanamide



N-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}-2,2-dimethylpropanamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.050 g, 0.09 mmol), 2,2-Dimethyl-propionyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-1,2-dimethylpropyl}-2,2-dimethylpropanamide(0.039 g, 67%) as an oil. ES-LCMS *m/z* 643 (M+1).

Example 924

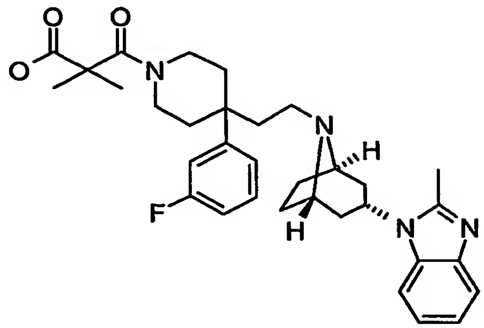
Preparation of 2,2-dichloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide



2,2-dichloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine(0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol)and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2-dichloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-1,2-dimethylpropyl}acetamide(0.042 g, 69%) as an oil. ES-LCMS *m/z* 643 (M+1).

Example 925

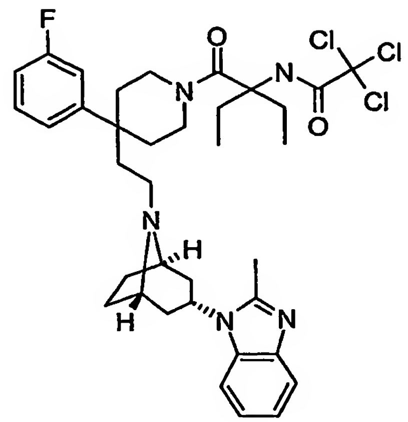
Preparation of 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoic acid



3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoic acid was obtained from 3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid, Example 628, (0.029 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5 to produce ethyl 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoate. Ethyl 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoate (0.100 g, 0.170 mmol), 5 N NaOH (10 ml) and ethanol (4 ml) was stirred at 90°C for 3 hrs. The reaction was evaporated to dryness and residue was suspend in water (10 ml) and neutralized with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was dried using magnesium sulfate and concentrated down to form the title compound as a white solid (0.081 g, 85%). ES-LCMS *m/z* 561 (M+1).

Example 926

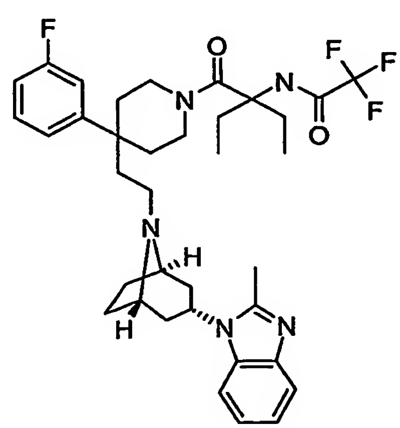
Preparation of 2,2,2-trichloro-*N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]propyl}acetamide



2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.100 g, 0.178 mmol), trichloroacetyl chloride (0.032 g, 0.178 mmol)and DIEA (0.069 g, 0.534 mmol) as outlined in procedure for procedure for **Example 890** to give title compound, 2,2,2-trichloro-*N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]propyl}acetamide(0.068 g, 54%). ES-LCMS *m/z* 706 (M+1).

Example 927

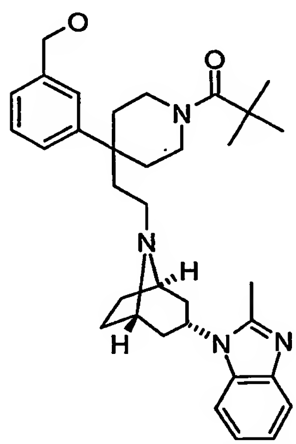
Preparation of *N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]propyl}-2,2,2-trifluoroacetamide



2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one example 890 (0.100 g, 0.178 mmol), trifluoroacetic anhydirde (0.038 g, 0.178 mmol)and DIEA (0.069 g, 0.534 mmol) as outlined in procedure for procedure for Example 890 to give title compound, *N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]propyl}-2,2,2-trifluoroacetamide(0.061 g, 52%). ES-LCMS *m/z* 656 (M+1).

Example 928

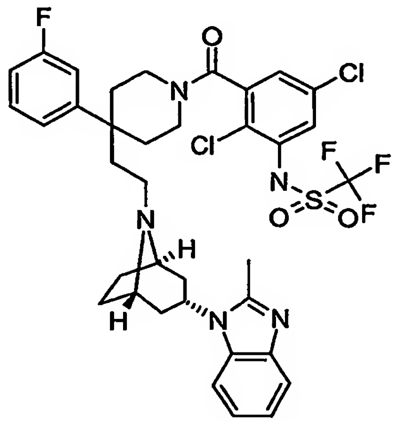
Preparation of [3-(1-(2,2-dimethylpropanoyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-piperidinyl)phenyl]methanol



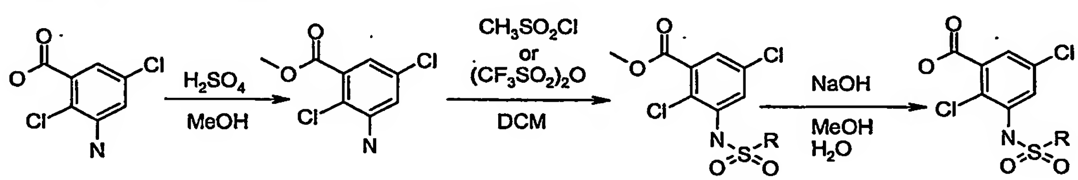
[3-(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-piperidinyl) phenyl]methanol dihydrochloride(0.100 g, 0.188 mmol), Dimethyl-propionyl chloride(0.024 g, 0.188 mmol) and DIEA (0.069 g, 0.534 mmol) were stirred at room temperature in DCM (3 ml) for 2 hours. Solvent was removed and compound was purified by RP-HPLC to give the title compound, [3-(1-(2,2-dimethylpropanoyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-piperidinyl)phenyl]methanol (0.069 g, 71%). ES-LCMS *m/z* 543 (M+1).

Example 929

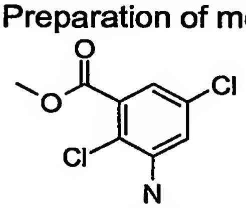
Preparation of *N*-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl] phenyl}-1,1,1-trifluoromethanesulfonamide



N-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl] phenyl}-1,1,1-trifluoromethanesulfonamide was obtained through procedure outlined in scheme.

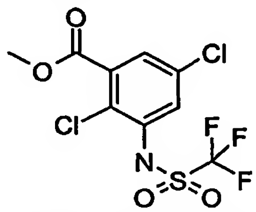


Preparation of methyl 3-amino-2,5-dichlorobenzoate



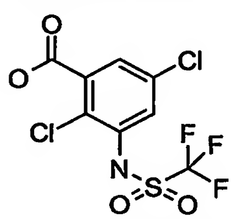
3-amino-2,5-dichlorobenzoic acid(5.00 g, 24.27 mmol) was stirred in methanol(30 ml) at room temperature. Sulfuric Acid(5 ml) was added dropwise. Reaction stirred for 3 hours and was then diluted with water(30 ml) and basified using sodium hydroxide. Mixture was extracted with ethyl acetate x 3. Solvent was removed to afford methyl 3-amino-2,5-dichlorobenzoate(4.20 g, 79%) as a solid.

Preparation of methyl 2,5-dichloro-3-{[(trifluoromethyl) sulfonyl]amino}benzoate



methyl 3-amino-2,5-dichlorobenzoate(2.10 g, 9.55 mmol), DIEA(3.0 ml) were stirred in DCM(40 ml) at 0°C. Triflic anhydride(3.90 g, 14.31 mmol) was added dropwise whike stirring at 0°C. After 2hrs at 0°C, reaction was allowed to warm to room temperature while stirring overnight. Quenched rxn with saturated NH4Cl and washed with brine. Organic layer with dried to yeild crude methyl 2,5-dichloro-3-{[(trifluoromethyl) sulfonyl]amino}benzoate(4.0 g) which will be carried on.

Preparation of 2,5-dichloro-3-{[(trifluoromethyl) sulfonyl]amino}benzoic acid hydrochloride



Crude methyl 2,5-dichloro-3-{[(trifluoromethyl) sulfonyl]amino}benzoate(4.0 g) was dissolved in methanol(30 ml) and 4N NaOH(30 ml) was added while stirring at room temperature for 18 hrs. Removed solvent and added 4N HCl(10 ml). Stirred at room temperature for 4hours. Filtered off solid to give 2,5-dichloro-3-{[(trifluoromethyl) sulfonyl] amino}benzoic acid hydrochloride in quantitative yield.

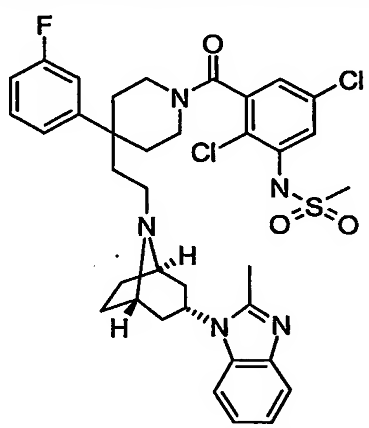
Preparation of example 929

N-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl] phenyl}-1,1,1-trifluoromethanesulfonamide (0.140 g, 47%)was obtained as a

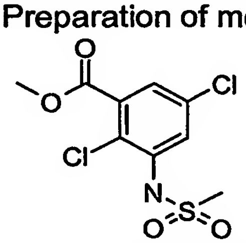
oil from (0.320 g, 1.4 mmol), 2,5-dichloro-3-{[(trifluoromethyl) sulfonyl] amino}benzoic acid hydrochloride(0.157 g, 0.46 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 766(M+1).

Example 930

Preparation of *N*-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl} methanesulfonamide



Preparation of methyl 2,5-dichloro-3-[(methylsulfonyl)amino]benzoate



From common intermediate methyl 3-amino-2,5-dichlorobenzoate following the procedure outlined in scheme. Methyl 3-amino-2,5-dichlorobenzoate(2.10 g, 9.55 mmol), DIEA(3.0 ml) were stirred in DCM(40 ml) at 0°C methanesulfonyl chloride (2.18 g, 19.08 mmol) was added dropwise whike stirring at 0°C. After 2hrs at 0°C, reaction was allowed to warm to room temperature while stirring overnight. Quenched rxn with saturated NH4Cl and

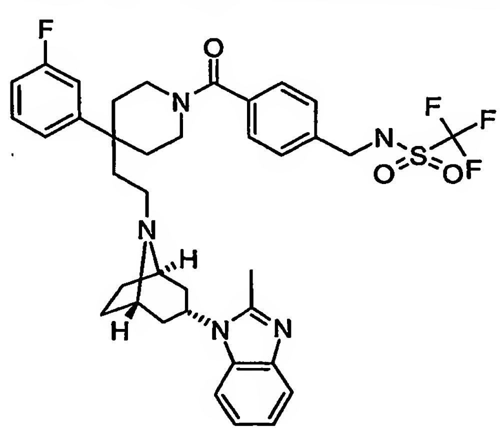
washed with brine. Organic layer with dried to yeild crude methyl 2,5-dichloro-3-[(methylsulfonyl)amino]benzoate(3.10 g) which will be carried on. methyl 2,5-dichloro-3-[(methylsulfonyl)amino]benzoate(3.10 g) was treated with NaOH, methanol following procedure outlined in scheme to form 2,5-dichloro-3-[(methylsulfonyl)amino]benzoic acid hydrochloride (3.53 g).

Preparation of example 930

N-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl} methanesulfonamide (0.127 g, 45%)was obtained as a oil from 2,5-dichloro-3-[(methylsulfonyl)amino]benzoic acid hydrochloride (0.132 g, 0.46 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 712(M+1).

Example 931

Preparation of 1,1,1-trifluoro-*N*-({4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]phenyl}methyl)methanesulfonamide

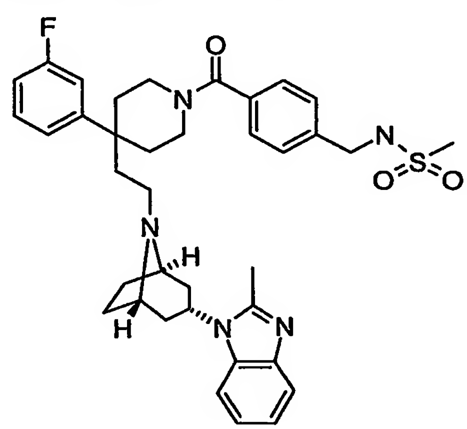


By the procedure outlined in example 929, starting from 4-(aminomethyl)benzoic acid(2.00 g, 13.24 mmol) was treated with sulfuric acid to form methyl 4-(aminomethyl)benzoate(1.20 g, 55%). Methyl 4-

(aminomethyl)benzoate(0.600 g, 3.63 mmol) was treated with triflic anhydride(1.512 g, 4.92 mmol) in DCM(20 ml) to give crude methyl 4-({[(trifluoromethyl)sulfonyl]amino}methyl) benzoate(0.402 g, 37%). Methyl 4-({[(trifluoromethyl) sulfonyl]amino}methyl) benzoate(0.402 g, 1.35 mmol) was treated with NaOH and methanol to give 4-({[(trifluoromethyl)sulfonyl]amino}methyl)benzoic acid hydrochloride(0.380 g, 95%). The title compound, 1,1,1-trifluoro-*N*-({4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]phenyl}methyl) methanesulfonamide(0.145 g, 52%) was obtained as a oil from 4-({[(trifluoromethyl)sulfonyl]amino}methyl)benzoic acid hydrochloride (0.157 g, 0.46l), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 712(M+1).

Example 932

Preparation of *N*-({4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methyl) methanesulfonamide

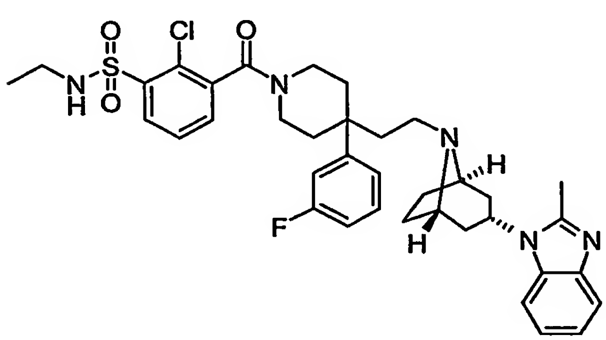


By the procedure outlined in scheme example 929, starting from 4-(aminomethyl)benzoic acid (2.00 g, 13.24 mmol) was treated with sulfuric acid to form methyl 4-(aminomethyl)benzoate(1.20 g, 55%). Methyl 4-(aminomethyl)benzoate (0.600 g, 3.63 mmol) was treated with

methanesulfonyl chloride (0.832 g, 7.26 mmol)) in DCM(20 ml) to give crude methyl 4-{[(methylsulfonyl)amino] methyl}benzoate(0.398 g, 45%). Methyl 4-{[(methylsulfonyl)amino]methyl}benzoate(0.398 g, 1.63 mmol) was treated with NaOH and methanol to give 4-{[(methylsulfonyl)amino]methyl}benzoic acid hydrochloride(0.370 g, 98%). The title compound, *N*-({4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methyl) methanesulfonamide
(0.128 g, 50%) was obtained as a oil from 4-{[(methylsulfonyl)amino]methyl}benzoic acid hydrochloride (0.132 g, 0.46l), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 658(M+1).

Example 933

Preparation of 2-chloro-***N***-ethyl-3-[(4-(3-fluorophenyl)-4-{2-[(1***R***,5***S***)-3-(2-methyl-1***H***-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



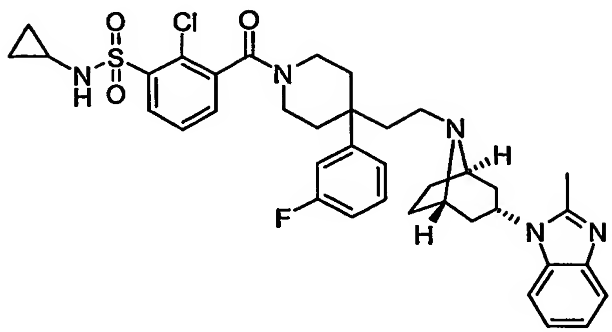
Preparation of 2-chloro-3-[(ethylamino)sulfonyl]benzoic acid. To a solution of methyl 2-chloro-3-(chlorosulfonyl)benzoate (608 mg, 2.26 mmol) and K_2CO_3 (770 mg, 5.6 mmol) in 10 mL benzene was added ethylamine (5.6 mL, 11.2 mmol). Purification of the product provided methyl 2-chloro-3-

[(ethylamino)sulfonyl]benzoate (335 mg, 53%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$), □ 8.24 (dd, 1H, J = 8.0, 1.7 Hz), 7.90 (dd, 1H, J = 7.8, 1.7 Hz), 7.47 (t, 1H, J = 7.8 Hz), 5.14 (t, 1H, J = 5.9 Hz), 3.94 (s, 3H), 2.98 (qd, 2H, J = 7.3, 6.0 Hz), 1.09 (t, 3H, J = 7.2 Hz); ESI-MS 278 (M+H), 300 (M+Na). Methyl 2-chloro-3-[(ethylamino)sulfonyl]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(ethylamino)sulfonyl]benzoic acid as a solid, which was used without further purification. ESI-MS 264 (M+H), 286 (M+Na).

2-chloro-***N***-ethyl-3-[(4-(3-fluorophenyl)-4-{2-[(1***R***,5***S***)-3-(2-methyl-1***H***-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (282 mg, 83%) was obtained as a solid from 2-chloro-3-[(ethylamino)sulfonyl]benzoic acid (51 mg, 0.19 mmol), 1-((1***R***,5***S***)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1***H***-benzimidazole dihydrochloride (117 mg, 0.19 mmol) and HATU (80 mg, 0.21 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 8.12 (m, 1 H), 7.64 (m, 1 H), 7.53-7.40 (m, 2 H), 7.38-7.25 (m, 2 H), 7.14 (m, 2 H), 7.05 (m, 1 H), 7.00-6.92 (m, 2 H), 5.80-5.35 (m, 2 H), 4.52 (m, 1 H), 4.20 (m, 1 H), 3.45-2.87 (m, 7 H), 2.52 (m, 3 H, rotamers), 2.40-1.60 (m, 15 H), 1.1 (m, 3H); ESI-MS 692 (M+H).

Example 934

Preparation of 2-chloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

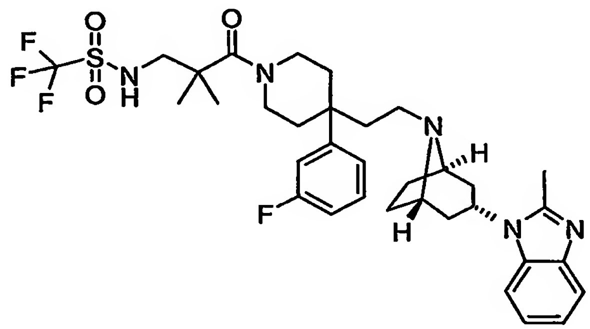


Preparation of 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoic acid. To a solution of methyl 2-chloro-3-(chlorosulfonyl)benzoate (608 mg, 2.26 mmol) and K_2CO_3 (770 mg, 5.6 mmol) in 10 mL benzene was added cyclopropylamine (0.78 mL, 11.2 mmol). Purification of the product provided methyl 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoate (355 mg, 54%) as a solid. ^1H NMR (400 MHz, $CDCl_3$), □ 8.28 (dd, 1H, J = 7.9, 1.7 Hz), 7.90 (dd, 1H, J = 7.8, 1.7 Hz), 7.48 (t, 1H, J = 7.8 Hz), 5.63 (s, 1H), 3.93 (s, 3H), 2.17 (m, 1H), 0.65-0.58 (m, 2H), 0.57-0.50 (m, 2H); ESI-MS 290 (M+H), 312 (M+Na). Methyl 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoic acid as a solid, which was used without further purification. ESI-MS 276 (M+H), 298 (M+Na).

2-chloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (288 mg, 91%) was obtained as a solid from 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoic acid (41 mg, 0.15 mmol), 1-((1***R***,5***S***)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (90 mg, 0.15 mmol) and HATU (62 mg, 0.16 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, $CDCl_3$),
□ 8.18 (m, 1H), 7.65 (m, 1H), 7.56-7.25 (m, 4H), 7.15 (m, 2H), 7.05 (m, 1H), 7.01-6.91 (m, 2H), 5.95-5.44 (m, 2H), 4.61 (m, 1H), 4.23 (m, 1H), 3.45-3.05 (m, 5H), 2.56 (s, 1.5H, rotamer), 2.54 (s, 1.5H, rotamer), 2.43-1.74 (m, 15H), 1.70-1.58 (m, 2H), 0.78 (m, 1H), 0.63-0.50 (m, 2H); ESI-MS 704 (M+H).

Example 935

Preparation of 1,1,1-trifluoro-*N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide



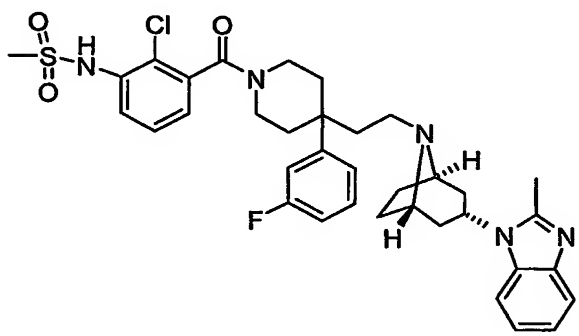
Preparation of 2,2-dimethyl-3-{[(trifluoromethyl)sulfonyl]amino}propanoic acid. To a –78 °C solution of methyl 3-amino-2,2-dimethylpropanoate (318 mg, 2.4 mmol) and Et_3N (0.34 mL, 2.44 mmol) in 4 mL CH_2Cl_2 was added trifluoromethanesulfonic anhydride (0.81 mL, 4.84 mmol). The reaction was stirred for 4h below –40 °C and quenched with saturated aqueous $NaHCO_3$. The crude methyl 2,2-dimethyl-3-{[(trifluoromethyl)sulfonyl]amino}propanoate was isolated and hydrolyzed using aqueous NaOH to provide 2,2-dimethyl-3-{[(trifluoromethyl)sulfonyl]amino}propanoic acid which was used without further purification.

1,1,1-trifluoro-*N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide (41 mg, 44%) was obtained as a solid from 2,2-dimethyl-3-{[(trifluoromethyl)sulfonyl]amino}propanoic acid (100 mg, 0.40 mmol), 1-((1***R***,5***S***)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1***H***-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, $CDCl_3$), □□.71-7.67 (m, 1H), 7.41-7.21 (m, 4H), 7.07 (m, 1H), 7.02-6.94 (m, 2H), 4.84 (q, 1H, J = 9.5 Hz), 3.94 (m, 2H),

3.45 (m, 2H), 3.21 (m, 5H), 2.62 (s, 3H), 2.54 (m, 2H), 2.20 (m, 2H), 2.14-1.95 (m, 6H), 1.87 (m, 2H), 1.81-1.71 (m, 4H), 1.33 (s, 6H); ESI-MS 678 (M+H).

Example 936

Preparation of *N*-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



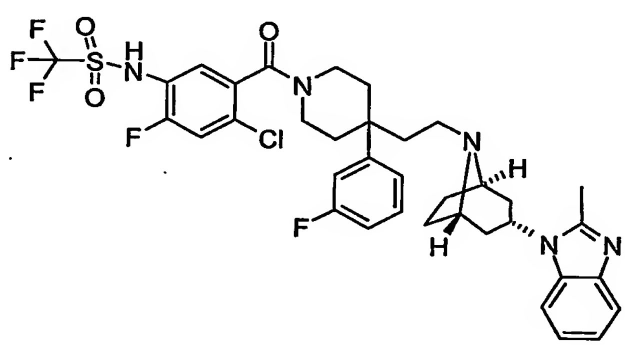
Preparation of 2-chloro-3-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 3-amino-2-chlorobenzoate (517 mg, 2.79 mmol) and pyridine (0.25 mL, 3.06 mmol) in 8mL CH_2Cl_2 was added methanesulfonylchloride (0.24 mL, 3.06 mmol). After washing with 1M HCl, methyl 2-chloro-3-[(methylsulfonyl)amino]benzoate was isolated as a solid in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.77 (dd, 1H, J = 8.2, 1.6 Hz), 7.61 (dd, 1H, J = 7.9, 1.6 Hz), 7.33 (t, 1H, J = 7.9 Hz), 7.16 (s, 1H), 3.91 (s, 3H), 2.99 (s, 3H); ESI-MS 262 (M-H). Methyl 2-chloro-3-[(methylsulfonyl)amino]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(methylsulfonyl)amino]benzoic acid as a solid, which was used without further purification. ESI-MS 248 (M-H).

N-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (18 mg, 20%) was obtained as a solid from 2-chloro-3-[(methylsulfonyl)amino]benzoic acid (49 mg, 0.20 mmol),

1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.72-7.63 (m, 2H), 7.41-7.25 (m, 4H), 7.16 (m, 2H), 7.07 (m, 1H), 7.02-6.93 (m, 2H), 4.62 (m, 1H), 4.22 (m, 1H), 3.48-3.09 (m, 5H), 3.07 (2, 1.5H, rotamer), 3.04 (s, 1.5H, rotamer), 2.58-2.53 (m, 3H, rotamers), 2.45-2.24 (m, 3H), 2.18-1.61 (m, 15H); ESI-MS 678 (M+H).

Example 937

Preparation of *N*-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide



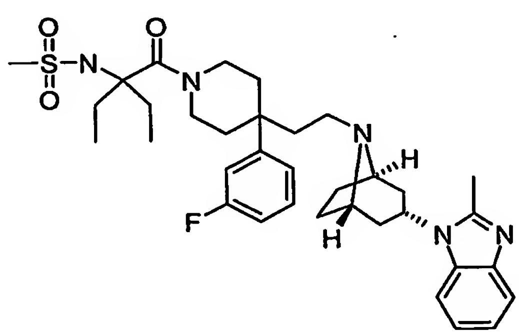
Preparation of 2-chloro-4-fluoro-5-{[(trifluoromethyl)sulfonyl]amino}benzoic acid. To a –78 °C solution of methyl 5-amino-2-chloro-4-fluorobenzoate (195 mg, 1.0 mmol) and Et_3N (0.13 mL, 1.0 mmol) in 2 mL CH_2Cl_2 was added trifluoromethanesulfonic anhydride (0.32 mL, 1.9 mmol). The reaction was stirred for 4h below –40 °C and quenched with saturated aqueous $NaHCO_3$. The crude methyl 2-chloro-4-fluoro-5-{[(trifluoromethyl)sulfonyl]amino}benzoate (ESI-MS 336 (M+H)) was isolated and hydrolyzed using aqueous NaOH to provide 2-chloro-4-fluoro-5-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (ESI-MS 320 (M-H)) which was used without further purification.

N-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (27 mg, 26%) was obtained as a solid from 2-chloro-4-fluoro-5-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (90 mg, 0.28 mmol), 1-((1***R***,5***S***)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$),

□ 7.68 (m, 1H), 7.58-7.46 (m, 1H), 7.38 (m, 1H), 7.31-7.19 (m, 3H), 7.14 (m, 1H), 7.08-6.93 (m, 3H), 5.06 (m, 1H), 4.12 (m, 1H), 3.89-3.63 (m, 2H), 3.48-3.08 (m, 4H), 2.77-2.33 (m, 7H), 2.30-1.76 (m, 12H); ESI-MS 750 (M+H).

<u>Example 938</u>

<u>Preparation of *N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]propyl}methanesulfonamide</u>



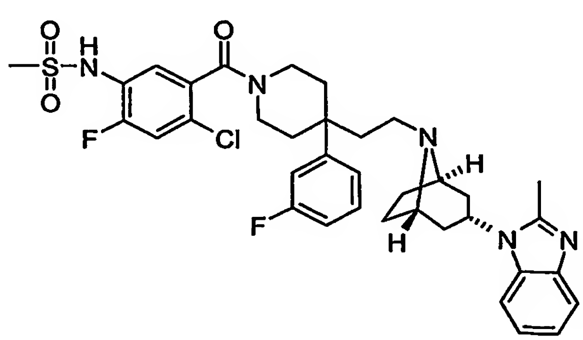
<u>Preparation of 2-ethyl-2-[(methylsulfonyl)amino]butanoic acid.</u> To a solution of 0 °C solution of diethylglycine (205 mg, 1.56 mmol) in 2mL 1M NaOH was added methanesulfonyl chloride (0.14 mL, 1.81 mmol) with periodic stirring and addition of another 2mL 1M NaOH. The reaction mixture was stirred for 1h at 0 °C, 4h at room temperature, and then acidified with 1M HCl and extracted into EtOAc to provide the crude 2-ethyl-2-

[(methylsulfonyl)amino]butanoic acid (37 mg, 11%) as a solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$), □ 5.19 (s, 1H), 3.06 (s, 3H), 2.14 (m, 2H), 1.92 (m, 2H), 0.96 (t, 6H, J = 7.4 Hz).

N-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]propyl}methanesulfonamide (69 mg, 79%) was obtained as a solid from 2-ethyl-2-[(methylsulfonyl)amino]butanoic acid (37 mg, 0.18 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.65-7.62 (m, 1H), 7.39-7.30 (m, 1H), 7.28 (m, 1H), 7.19-7.11 (m, 2H), 7.06 (m, 1H), 7.01-6.91 (m, 2H), 6.35 (s, 0.3H, rotamer), 6.28 (s, 0.7H, rotamer), 4.75 (br. s, 1H), 4.07-3.96 (m, 2H), 3.39-3.25 (m, 4H), 2.98 (s, 2H, rotamer), 2.97 (s, 1H, rotamer), 2.57 (s, 3H), 2.48-2.38 (m, 2H), 2.31 (m, 2H), 2.24-2.15 (m, 2H), 2.01-1.91 (m, 4H), 1.90-1.74 (m, 8H), 1.74-1.63 (m, 2H), 0.96-0.85 (m, 6H); ESI-MS 638 (M+H).

Example 939

Preparation of *N*-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide

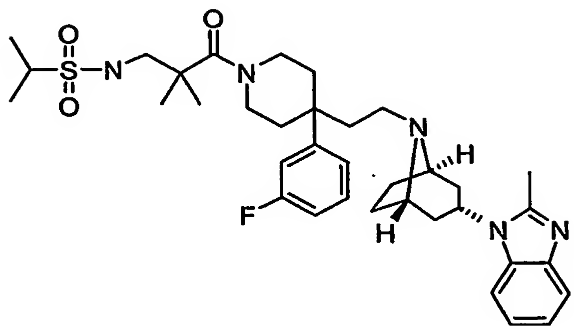


Preparation of 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 5-amino-2-chloro-4-fluorobenzoate (152 mg, 0.75 mmol) and pyridine (0.07 mL, 0.82 mmol) in 3 mL CH_2Cl_2 was added methanesulfonyl chloride (0.06 mL, 0.82 mmol). After 3 days at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and filtered through a silica plug to provide methyl 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoate (96 mg, 44%) as a solid (ESI-MS 280 (M-H)), which was hydrolyzed using aqueous NaOH to provide 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoic acid (ESI-MS 266 (M-H)), which was used without further purification.

N-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (15.9 mg, 7%) was obtained as a solid from 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoic acid (91 mg, 0.34 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (210 mg, 0.34 mmol) and HATU (194 mg, 0.51 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, $CDCl_3$), □ 7.66 (m, 1H), 7.55 (m, 0.5H, rotamer), 7.42-7.32 (m, 1.5H, rotamer), 7.31-7.27 (m, 1H), 7.25-7.11 (m, 3H), 7.07 (m, 1H), 7.02-6.93 (m, 2H), 4.65 (br. s, 1H), 4.29-4.11 (m, 1H), 3.47-3.11 (m, 5H), 3.08 (s, 1.5H, rotamer), 3.05 (s, 1.5H, rotamer), 2.56 (s, 3H), 2.46-2.35 (m, 2H), 2.33-2.24 (m, 1H), 2.18-2.10 (m, 1H), 2.00-1.73 (m, 10H), 1.67 (m, 2H); ESI-MS 696 (M+H).

Example 940

Preparation of *N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]propane-2-sulfonamide

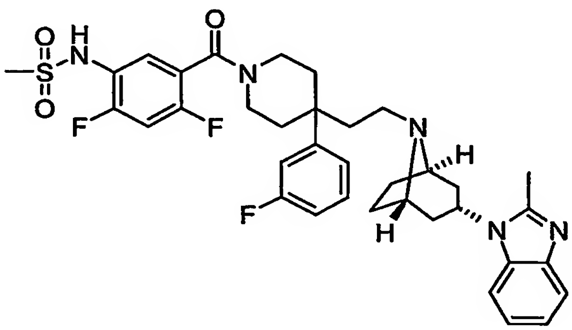


Preparation of 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoic acid. To a solution of methyl 3-amino-2,2-dimethylpropanoate (200 mg, 1.53 mmol) and Et_3N (0.64 mL, 4.59 mmol) in 2 mL CH_2Cl_2 was added isopropylsulfonyl chloride (0.34 mL, 3.05 mmol). The reaction was stirred for 24h, quenched by the addition of saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, and chromatographed (1:1 hex:EtOAc) to provide methyl 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoate (77 mg, 21%) as a solid. ^1H NMR (400 MHz, $CDCl_3$), 4.78 (t, 1H, J = 6.6 Hz), 3.68 (s, 3H), 3.20-3.11 (m, 3H), 1.36 (d, 6H, J = 6.9 Hz), 1.23 (s, 6H). Methyl 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoate was hydrolyzed using aqueous NaOH to provide 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoic acid, which was used without further purification.

N-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]propane-2-sulfonamide (130mg, 74%) was obtained as a solid from 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoic acid (60 mg, 0.27 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (164 mg, 0.27 mmol) and HATU (154 mg, 0.41 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, $CDCl_3$), □ 7.68-7.64 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.16 (m, 2H), 7.08 (m, 1H), 7.00 (m, 1H), 6.96 (m, 1H), 5.36 (t, 1H, J = 6.6 Hz), 4.65 (br. s, 1H), 3.93 (m, 2H), 3.33-3.20 (m, 4H), 3.15 (m, 1H), 3.10 (m, 2H), 2.58 (s, 3H), 2.40 (m, 2H), 2.19 (m, 2H), 2.00-1.73 (m, 10H), 1.67 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.33 (s, 6H); ESI-MS 652 (M+H).

Example 941

Preparation of *N*-{2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



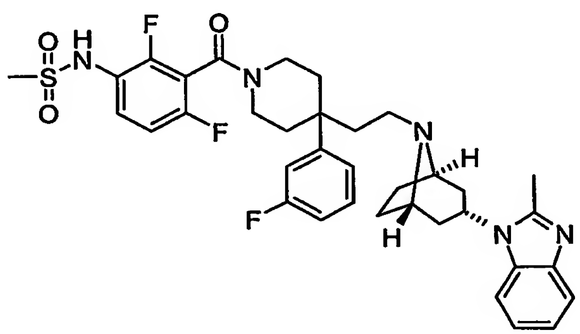
Preparation of 2,4-difluoro-5-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 5-amino-2,4-difluorobenzoate (252 mg, 1.35 mmol) and pyridine (0.13 mL, 1.61 mmol) in 5 mL CH_2Cl_2 was added methanesulfonyl chloride (0.12 mL, 1.48 mmol). After 24h at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ to provide crude methyl 2, 4-difluoro-5-[(methylsulfonyl)amino]benzoate as a solid (ESI-MS 264 (M-H)), which was hydrolyzed using aqueous NaOH to provide 2,4-difluoro-5-[(methylsulfonyl)amino]benzoic acid (ESI-MS 250 (M-H)), which was used without further purification.

N-{2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (7.0 mg, 13%) was obtained as a solid from 2,4-difluoro-5-[(methylsulfonyl)amino]benzoic acid (20 mg, 0.08 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (48 mg, 0.08 mmol) and HATU (45 mg, 0.12 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.73-7.68 (m, 1H), 7.60 (s, 1H), 7.41 (m, 1H), 7.25-7.15 (m, 3H), 7.12-7.07 (m, 1H), 7.04-6.93 (m, 3H), 4.26-4.11 (m, 1H), 3.89-3.63 (m, 2H), 3.58-3.43 (m, 2H), 3.29-3.16 (m, 2H), 3.07

(s, 2H, rotamer), 3.02 (s, 1H, rotamer), 2.70 (s, 3H), 2.41-1.61 (m, 16H); ESI-MS 681 (M+H).

Example 942

Preparation of *N*-{2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



Preparation of 2,6-difluoro-3-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 3-amino-2,6-difluorobenzoate (530 mg, 2.83 mmol) and pyridine (0.28 mL, 3.40 mmol) in 10 mL CH_2Cl_2 was added methanesulfonyl chloride (0.24 mL, 3.11 mmol). After 24h at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ to provide crude methyl 2,6-difluoro-3-[(methylsulfonyl)amino]benzoate as a solid (ESI-MS 264 (M-H)), which was hydrolyzed using aqueous NaOH to provide 2,6-difluoro-3-[(methylsulfonyl)amino]benzoic acid (ESI-MS 250 (M-H)), which was used without further purification.

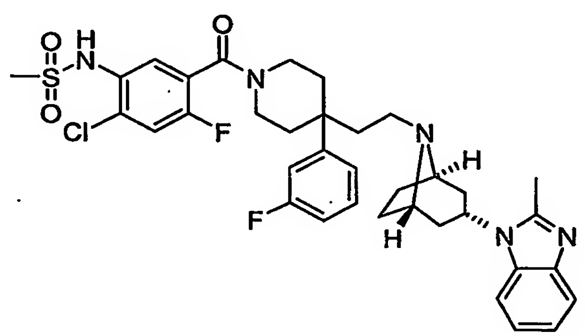
N-{2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (30.5 mg, 49%) was obtained as a solid from

2,6-difluoro-3-[(methylsulfonyl)amino]benzoic acid (26 mg, 0.10 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-

yl)-2-methyl-1*H*-benzimidazole dihydrochloride (56 mg, 0.09 mmol) and HATU (53 mg, 0.14 mmol) following the procedure outlined in example 5.
^{1}H NMR (400 MHz, $CDCl_3$), □ 7.79 (m, 1H), 7.55 (m, 1H), 7.42 (m, 1H), 7.34-7.23 (m, 3H), 7.13 (m, 1H), 7.05-6.94 (m, 3H), 6.02 (br. s, 1H), 4.13 (m, 1H), 3.98-3.80 (m, 2H), 3.59-3.43 (m, 2H), 3.23 (m, 1H), 3.08 (s, 3H), 2.97-3.85 (m, 2H), 2.82 (s, 3H), 2.61-2.46 (m, 2H), 2.39-1.86 (m, 12H); ESI-MS 681 (M+H).

Example 943

Preparation of *N*-{2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide

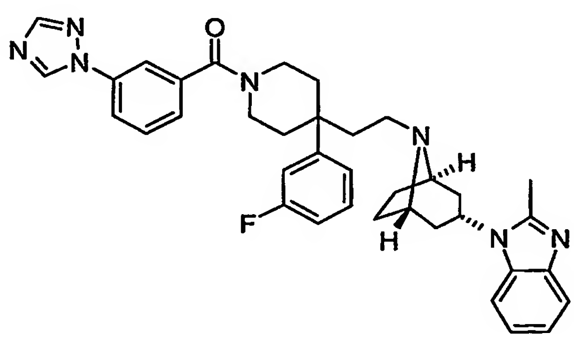


Preparation of 4-chloro-2-fluoro-5-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 5-amino-4-chloro-2-fluorobenzoate (248 mg, 1.22 mmol) and pyridine (0.12 mL, 1.46 mmol) in 5 mL CH_2Cl_2 was added methanesulfonyl chloride (0.10 mL, 1.34 mmol). After 5 days at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ to provide crude methyl 4-chloro-2-fluoro-5-[(methylsulfonyl)amino]benzoate as a solid (ESI-MS 280 (M-H)), which was hydrolyzed using aqueous NaOH to provide 4-chloro-2-fluoro-5-[(methylsulfonyl)amino]benzoic acid (ESI-MS 266 (M-H)), which was used without further purification.

N-{2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (56 mg, 59%) was obtained as a solid from 4-chloro-2-fluoro-5-[(methylsulfonyl)amino]benzoic acid (43 mg, 0.16 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.13 mmol) and HATU (78 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.68-7.61 (m, 1H), 7.61 (br. s, 1H), 7.36 (m, 1H), 7.31-7.26 (m, 1H), 7.25-7.21 (m, 1H), 7.21-7.12 (m, 2H), 7.07 (m, 1H), 7.02-6.93 (m, 2H), 4.68 (br. s, 1H), 4.19 (m, 1H), 3.50-3.15 (m, 5H), 3.04 (s, 3H), 2.58 (s, 3H), 2.51-2.34 (m, 2H), 2.28 (m, 2H), 2.15 (m, 2H), 2.07-1.76 (m, 10H), 1.69 (m, 2H); ESI-MS 696 (M+H).

Example 944

Preparation of 1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[3-(1*H*-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole

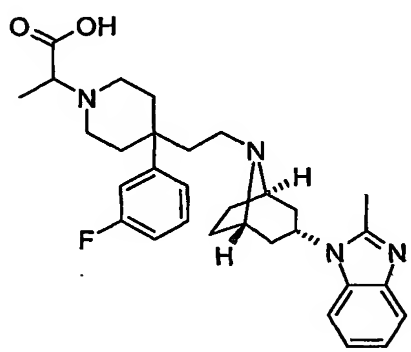


1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[3-(1*H*-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (89 mg, 47%) was obtained as a solid from 3-(1*H*-1,2,4-triazol-1-yl)benzoic acid (107 mg, 0.56 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (160 mg, 0.31 mmol) and HATU (176 mg, 0.46 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz,

$CDCl_3$), □ 8.58 (s, 1H), 8.11 (s, 1H), 7.77-7.72 (m, 2H), 7.67 (d, 1H, J = 7.9 Hz), 7.56 (t, 1H, J = 7.8 Hz), 7.43-7.24 (m, 3H), 7.17 (m, 2H), 7.09 (d, 1H, J = 7.7 Hz), 7.04-6.94 (m, 2H), 4.61 (m, 1H), 4.19 (m, 1H), 3.60 (m, 1H), 3.47-3.17 (m, 3H), 2.56 (s, 3H), 2.43-2.26 (m, 3H), 2.13 (m, 1H), 2.02-1.55 (m, 12H); ESI-MS 618 (M+H).

Example 945

Preparation of 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoic acid



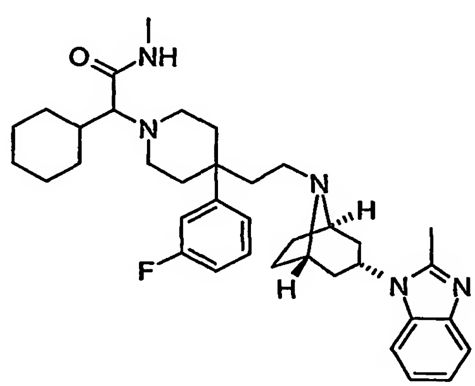
To a –78 °C solution of benzyl 2-hydroxypropanoate (250 mg, 1.39 mmol) and 4A molecular sieves in 2 mL CH_2Cl_2 was added trifluoromethanesulfonic anhydride (0.33 mL, 1.97 mmol). After stirring for 10 min at this temperature, 2,6-lutidine (0.31 mL, 2.62 mmol) was added. After 15 min, diisopropylethylamine (0.46 mL, 2.62 mmol) was added and after another 15 min, a solution of 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (400 mg, 0.66 mmol) in 3 mL CH_2Cl_2 was added. The reaction mixture was stirred at –78 °C, then allowed to warm to room temperature overnight, washed with saturated aqueous $NaHCO_3$, and purified by chromatographaphy (3% (2M NH_3 / MeOH) in $CHCl_3$) to provide benzyl 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoate (146 mg, 37%) as a solid. ^1H NMR (400 MHz, $CDCl_3$), □ 7.68

(m, 1H), 7.37-7.26 (m, 7H), 7.22-7.13 (m, 2H), 7.08 (m, 1H), 6.98 (m, 1H), 6.92 (m, 1H), 5.09 (s, 2H), 4.62 (m, 1H), 3.39-3.17 (m, 2H), 2.89-1.26 (m, 27H); ESI-MS 609 (M+H).

A solution of benzyl 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoate (136 mg, 0.223 mmol) in 8mL MeOH was stirred for 3h under an atmospheric pressure of hydrogen and in the presence of catalytic 5% Pd/C. Filtration and evaporation afforded 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoic acid (90.0 mg, 78%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.69 (m, 1H), 7.40 (m, 1H), 7.26-7.12 (m, 4H), 7.09-6.95 (m, 2H), 5.37 (m, 1H), 3.85-3.55 (m, 5H), 2.81-1.77 (18H), 2.62 (s, 3H), 1.61-1.41 (3H); ESI-MS 517 (M-H).

Example 946

Preparation of 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-*N*-methylacetamide



Preparation of cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid.

To a –78 °C solution of benzyl cyclohexyl(hydroxy)acetate (61 mg, 0.25 mmol) and 4A molecular sieves in 1.2 mL CH_2Cl_2 was added

trifluoromethanesulfonic anhydride (0.05 mL, 0.30 mmol). After stirring for 10 min at this temperature, 2,6-lutidine (0.06 mL, 0.49 mmol) was added. After 15 min, diisopropylethylamine (0.09 mL, 0.49 mmol) was added and after another 15 min, a solution of 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (153 mg, 0.30 mmol) in 1 mL CH_2Cl_2 was added. The reaction mixture was stirred at –78 °C, then allowed to warm to room temperature overnight, washed with saturated aqueous $NaHCO_3$, and purified by preparatory TLC using 5% MeOH in $CHCl_3$ to afford benzyl cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetate (33 mg, 20%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.68 – 7.64 (m, 1H), 7.33-7.23 (m, 7H), 7.20-7.12 (m, 2H), 7.05 (m, 1H), 6.97 (m, 1H), 6.89 (m, 1H), 5.05 (AB_q, 2H, J = 12.3 Hz), 4.61 (m, 1H), 3.26-3.18 (m, 2H), 2.92 (d, 1H, J = 10.4 Hz), 2.70 (m, 1H), 2.64-2.50 (m, 2H), 2.57 (s, 3H), 2.46-2.30 (m, 3H), 2.12-0.81 (m, 25H); ESI-MS 677 (M+H).

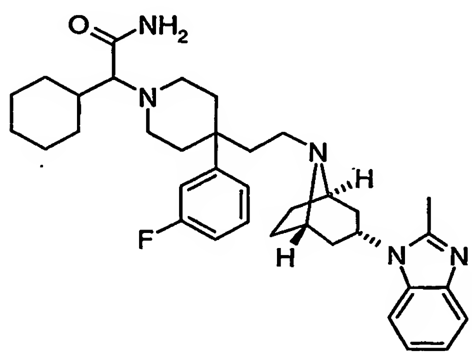
A solution of benzyl cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetate (23.8 mg, 0.035 mmol) in 3mL MeOH was stirred for 3h under an atmospheric pressure of hydrogen and in the presence of catalytic 5% Pd/C. Filtration and evaporation afforded cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (17.5 mg, 85%). ESI-MS 585 (M-H).

To a solution of cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (22.0 mg, 0.037 mmol), methylamine (0.056 mL of a 2M solution in THF, 0.11 mmol), N-hydroxybenzotriazole (10.1 mg, 0.075 mmol) and N-methylmorpholine (0.10 mL, 0.094 mmol) in 1 mL DMF was added EDC (14 mg, 0.075 mmol). The reaction mixture was stirred for 24h, then diluted with 4:1 EtOAc:hex and washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4)

and chromatographed (5% (2M NH_3 / MeOH) in $CHCl_3$) to provide 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-*N*-methylacetamide (8.1 mg, 36%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.66 (m, 1H), 7.33-7.27 (m, 2H), 7.20-7.11 (m, 2H), 7.05 (m, 1H), 6.98 (m, 1H), 6.90 (m, 1H), 4.64 (m, 1H), 3.33-3.20 (m, 2H), 2.80 (d, 3H, J = 4.9 Hz), 2.59 (s, 3H), 2.47-0.79 (m, 27H); ESI-MS 600 (M+H).

Example 947

Preparation of 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetamide

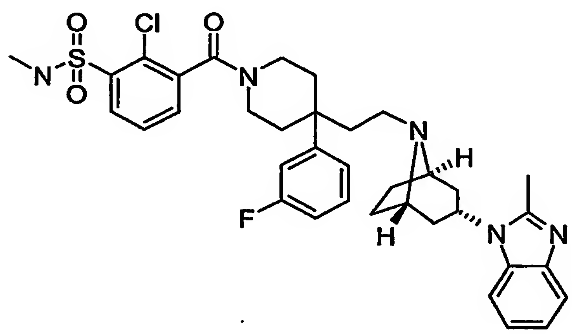


To a solution of cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (22.0 mg, 0.037 mmol), hydroxylamine (0.2 mL of a 28% solution in water, 3.3 mmol), N-hydroxybenzotriazole (10.1 mg, 0.075 mmol) and N-methylmorpholine (0.10 mL, 0.094 mmol) in 1 mL DMF was added EDC (14 mg, 0.075 mmol). The reaction mixture was stirred for 24h, then diluted with 4:1 EtOAc:hex and washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and chromatographed (5% (2M NH_3 / MeOH) in $CHCl_3$) to provide 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetamide

(7.7 mg, 35%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.66 (m, 1H), 7.34-7.27 (m, 2H), 7.20-7.12 (m, 2H), 7.06 (m, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 4.61 (m, 1H), 3.27-3.19 (m, 2H), 2.73-2.62 (m, 2H), 2.58 (s, 3H), 2.47-0.78 (m, 27H); ESI-MS 589 (M+H)

Example 948

Preparation of 2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide



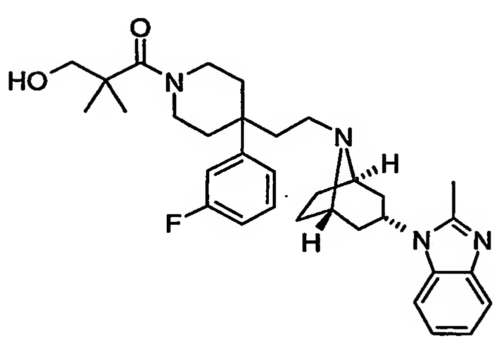
Preparation of 2-chloro-3-[(methylamino)sulfonyl]benzoic acid. To a solution of

To a solution of methyl 2-chloro-3-(chlorosulfonyl)benzoate (608 mg, 2.26 mmol) and K_2CO_3 (770 mg, 5.6 mmol) in 10 mL benzene was added a 2M solution of methylamine in THF (5.6 mL, 11.2 mmol). Purification of the product (2:1 hex:EtOAc) provided methyl 2-chloro-3-[(methylamino)sulfonyl]benzoate (430 mg, 72%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$), □ 8.23 (dd, 1H, J = 7.9, 1.7 Hz), 7.90 (dd, 1H, J = 7.8, 1.7 Hz), 7.48 (t, 1H, J = 7.9 Hz), 5.16 (q, 1H, J = 5.2 Hz), 3.94 (s, 3H), 2.62 (d, 3H, J = 5.3 Hz); ESI-MS 264 (M+H). Methyl 2-chloro-3-[(methylamino)sulfonyl]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(methylamino)sulfonyl]benzoic acid as a solid, which was used without further purification. ESI-MS 250 (M+H), 272 (M+Na).

2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide (87 mg, 62%) was obtained as a solid from 2-chloro-3-[(methylamino)sulfonyl]benzoic acid (52 mg, 0.21 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (127 mg, 0.21 mmol) and HATU (87 mg, 0.23 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 8.40 (m, 1H), 7.62 (m, 1H), 7.53-7.28 (m, 4H), 7.13 (m, 2H), 7.04 (m, 1H), 6.99-6.90 (m, 2H), 5.92-5.59 (m, 2H), 4.60 (m, 1H), 4.2 (m, 1H), 3.42-3.03 (m, 6H), 2.63-2.58 (m, 3H, rotamers), 2.54 (s, 1.5H, rotamer), 2.52 (s, 1.5H, rotamer), 2.41-2.23 (m, 3H), 2.17-1.58 (m, 11H); ESI-MS 678 (M+H).

Example 949

Preparation of 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol

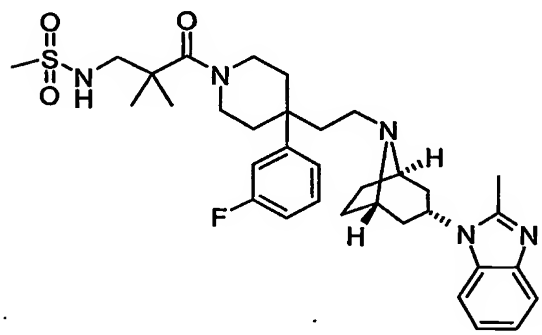


3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol (63 mg, 88%) was obtained as a solid from 3-hydroxy-2,2-dimethylpropanoic acid (23 mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (80 mg, 0.13 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.67-7.63

(m, 1H), 7.38-7.28 (m, 2H), 7.15 (m, 2H), 7.08 (m, 1H), 7.02-6.92 (m, 2H), 4.60 (m, 1H), 3.90 (m, 2H), 3.72 (m, 1H), 3.45 (m, 2H), 3.25 (m, 4H), 2.57 (s, 3H), 2.37 (m, 2H), 2.19 (m, 2H), 1.99-1.85 (m, 6H), 1.85-1.74 (m, 4H), 1.63 (m, 2H), 1.26 (s, 6H); ESI-MS 547 (M+H).

Example 950

Preparation of *N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide

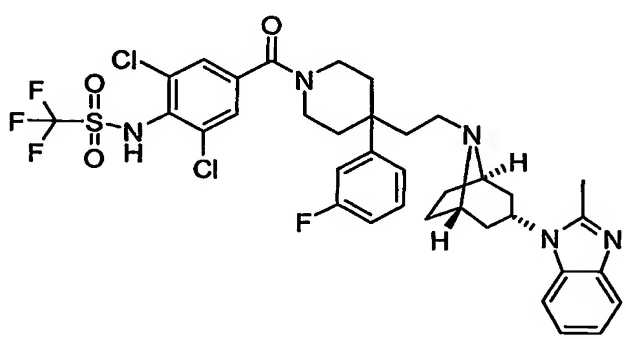


Preparation of 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoic acid. To a solution of methyl 3-amino-2,2-dimethylpropanoate (249 mg, 1.90 mmol) and Et_3N (0.80 mL, 5.70 mmol) in 2 mL CH_2Cl_2 was added methanesulfonyl chloride (0.29 mL, 3.80 mmol). The reaction was stirred for 2 days, quenched by the addition of saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, and chromatographed (1:1 hex:EtOAc) to provide methyl 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoate (124 mg, 31%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$), 4.95 (t, 1H, J = 6.8 Hz), 3.69 (s, 3H), 3.16 (d, 2H, J = 6.8 Hz), 2.95 (s, 3H), 1.24 (s, 6H). Methyl 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoate was hydrolyzed using aqueous NaOH to provide 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoic acid, which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$), □ 10.28 (br. s, 1H), 5.56 (br. s, 1H), 3.14 (s, 2H), 2.94 (s, 3H), 1.25 (s, 6H).

N-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide (41 mg, 48%) was obtained as a solid from 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoic acid (38 mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.63 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.14 (m, 2H), 7.06 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 5.52 (t, 1H, J = 6.8 Hz), 4.63 (m, 1H), 3.89 (m, 2H), 3.24 (m, 4H), 3.08 (d, 2H, J = 6.8 Hz), 2.93 (s, 3H), 2.56 (s, 3H), 2.37 (m, 2H), 2.18 (m, 2H), 1.92 (m, 6H), 1.78 (m, 4H), 1.64 (m, 2H), 1.32 (s, 6H); ESI-MS 624 (M+H).

Example 951

Preparation of *N*-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide

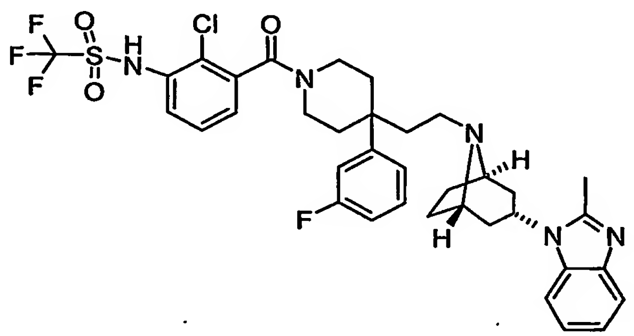


N-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (63 mg, 60%) was obtained as an oil from 3,5-dichloro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (70 mg, 0.21 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.68-7.64 (m, 1H), 7.37-7.25 (m, 4H), 7.18 (m, 2H), 7.08 (m, 1H), 7.01-6.90 (m, 2H), 5.17 (m, 1H), 4.02 (m, 1H), 3.52 (m, 1H), 3.30 (m, 2H), 2.64 (s, 3H), 2.56 (m, 2H), 2.23-1.69 (m, 13H); ESI-MS 766 (M+H).

Example 952

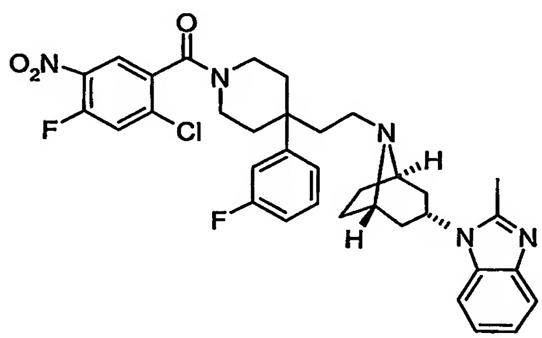
Preparation of *N*-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide



N-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (12 mg, 12%) was obtained as a solid from 2-chloro-3-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (66 mg, 0.22 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.70-7.64 (m, 1H), 7.58 (m, 1H), 7.42-7.28 (m, 2H), 7.25-6.92 (m, 5H), 6.88-6.74 (m, 2H), 5.00-4.70 (m, 1H), 4.32-4.00 (m, 1H), 3.75-3.00 (m, 5H), 2.58 (s, 3H), 2.32-1.20 (m, 17H); ESI-MS 732 (M+H).

Example 953

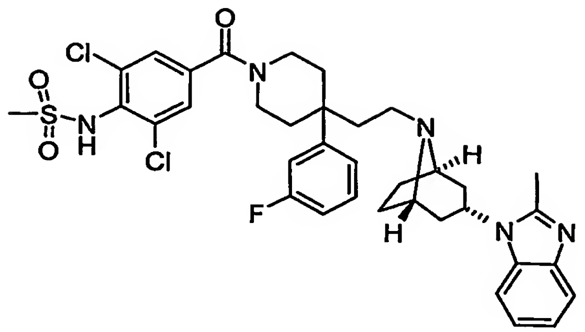
Preparation of 1-((1*R*,5*S*)-8-{2-[1-(2-chloro-4-fluoro-5-nitrobenzoyl)-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-((1*R*,5*S*)-8-{2-[1-(2-chloro-4-fluoro-5-nitrobenzoyl)-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (14 mg, 16%) was obtained as an oil from 2-chloro-4-fluoro-5-nitrobenzoic acid (39 mg, 0.18 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.66 (m, 1H), 7.43-7.27 (m, 3H), 7.16 (m, 2H), 7.07 (m, 1H), 7.03-6.93 (m, 3H), 4.62 (m, 1H), 4.24 (m, 1H), 3.46-3.07 (m, 6H), 2.57 (s, 3H), 2.44-1.59 (m, 15H); ESI-MS 648 (M+H).

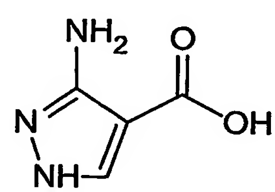
Example 954

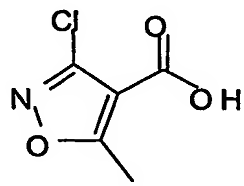
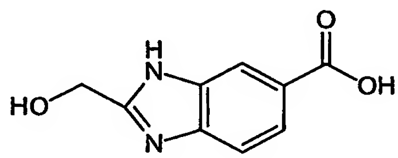
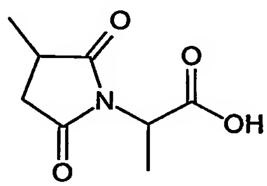
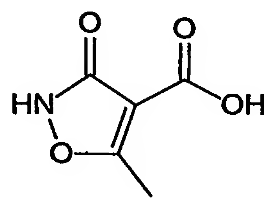
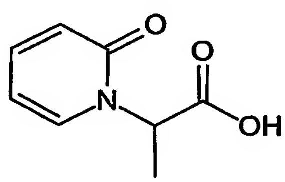
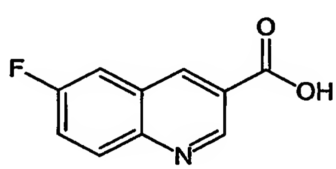
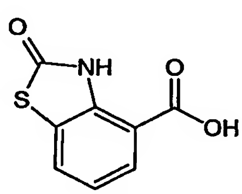
Preparation of *N*-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide

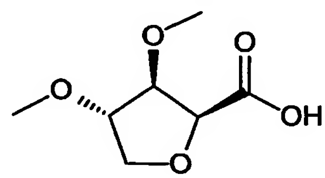
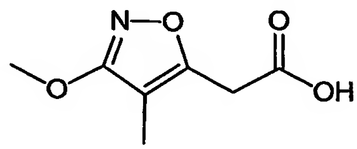
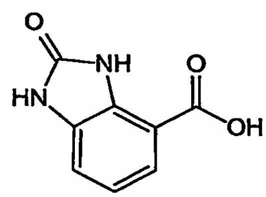
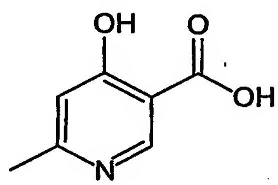
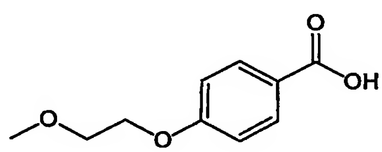
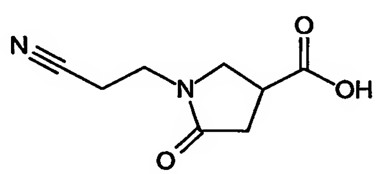
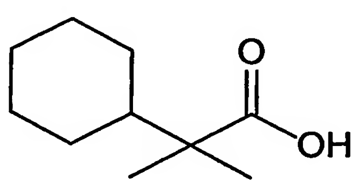


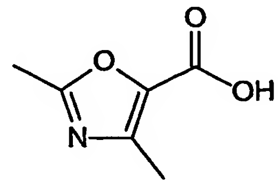
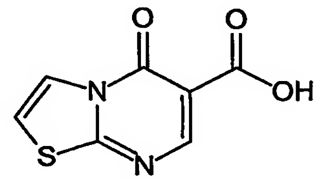
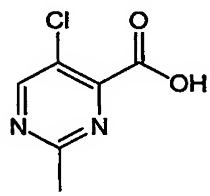
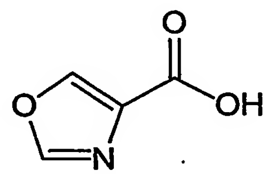
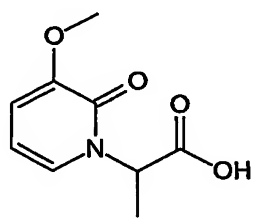
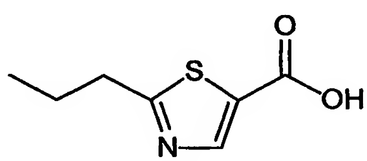
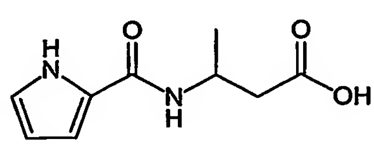
N-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (28 mg, 28%) was obtained as a solid from 3,5-dichloro-4-[(methylsulfonyl)amino]benzoic acid (59 mg, 0.21 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^{1}H NMR (400 MHz, $CDCl_3$), □ 7.62 (m, 1H), 7.37-7.22 (m, 3H), 7.13 (m, 2H), 7.05 (m, 1H), 7.01-6.88 (m, 3H), 4.58 (m, 1H), 4.12 (m, 1H), 3.55-3.22 (m, 5H), 3.21 (m, 3H, rotamers), 2.53 (m, 3H, rotamers), 2.41-1.56 (m, 15H); ESI-MS 712 (M+H).

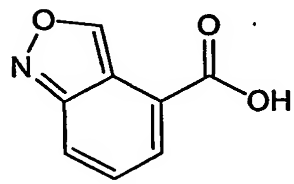
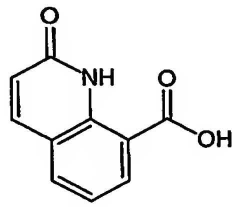
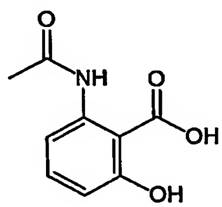
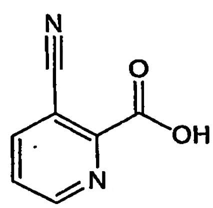
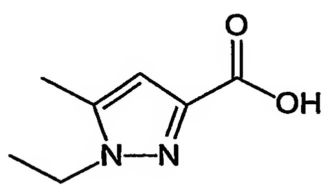
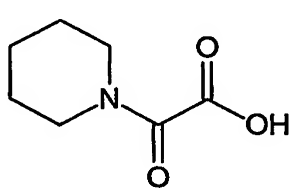
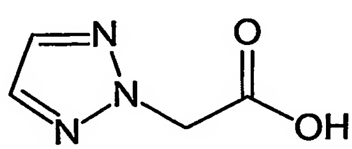
Additional examples of a the formula below were generated by coupling acids listed in the table using method A in example 5.

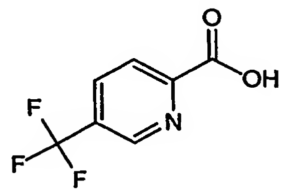
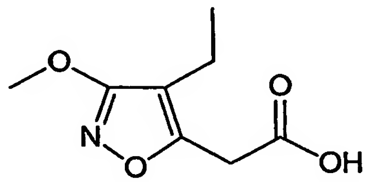
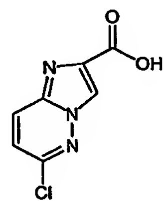
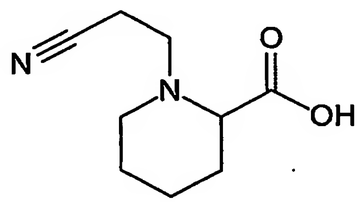
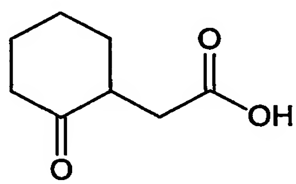
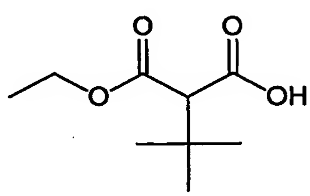
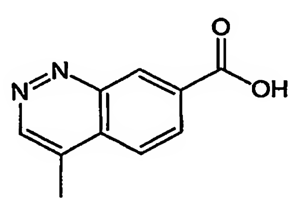
Example	% Yield	Acid	Method used	Observed mass (M+1)
958			A	556

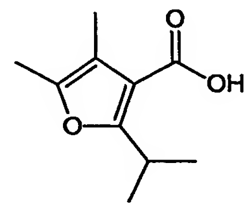
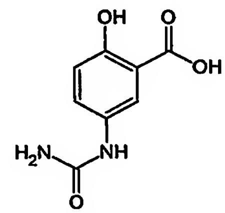
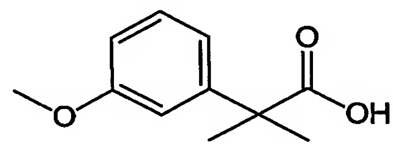
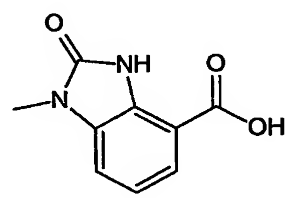
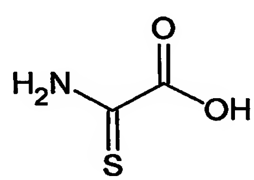
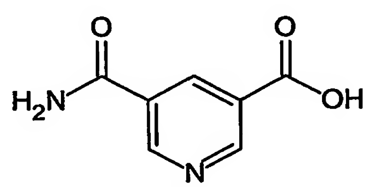
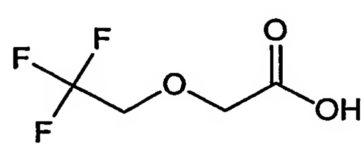
959	47		A	572
960	53		A	603
961	45		A	596
962	28		A	554
963	57		A	578
964	59		A	602
965	30		A	606

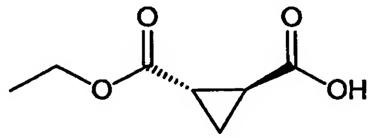
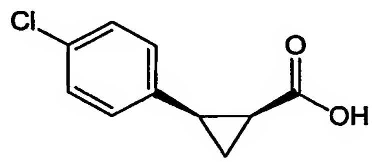
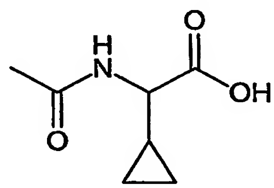
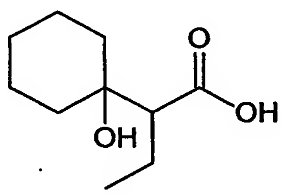
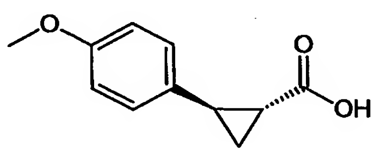
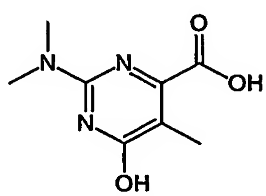
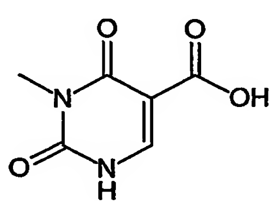
966	46		A	587
967	57		A	582
968	40		A	589
969	43		A	564
970	40		A	607
971	44		A	593
972	54		A	581

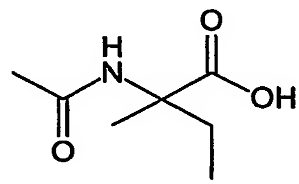
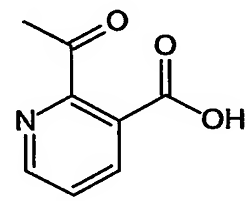
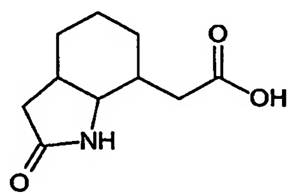
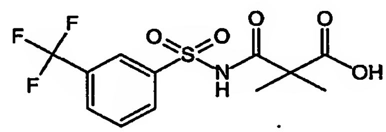
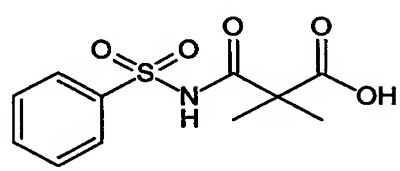
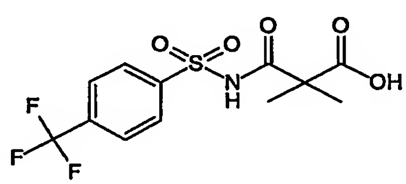
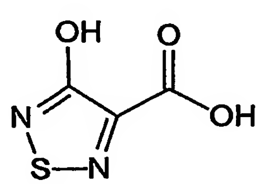
973	54		A	552
974	42		A	607
975	48		A	583
976	28		A	524
977	54		A	608
978	45		A	582
979	51		A	607

980	47		A	574
981	31		A	600
982	31		A	606
983	16		A	559
984	38		A	565
985	42		A	568
986	21		A	538

987	34		A	602
988	40		A	596
989	20		A	608
990	55		A	593
991	46		A	567
992	49		A	599
993	32		A	599

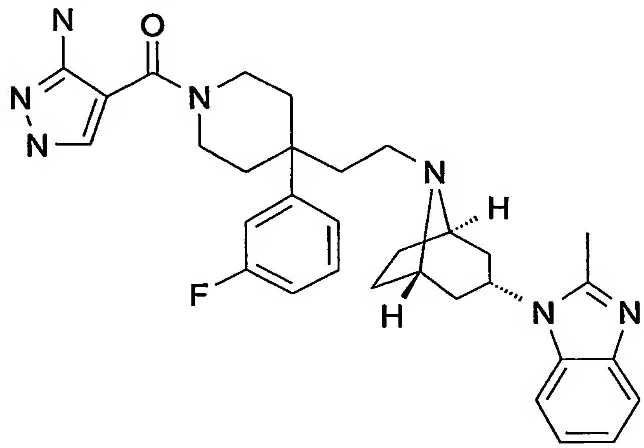
994	45		A	593
995	16		A	607
996	44		A	605
997	40		A	603
998	20		A	516
999	34		A	577
1000	33		A	569

1001	29		A	569
1002	45		A	607
1003	43		A	568
1004	45		A	597
1005	42		A	603
1006	16		A	608
1007	18		A	581

1008	21		A	570
1009	34		A	576
1010	43		A	608
1011			A	768
1012			A	700
1013			A	768
1014			A	575

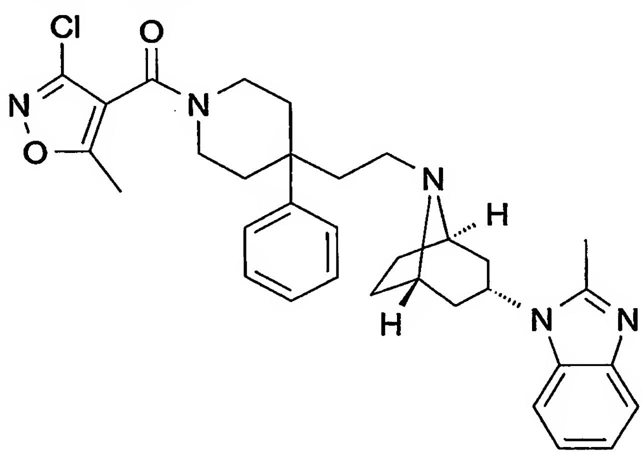
Example 958

4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1H-pyrazol-3-amine



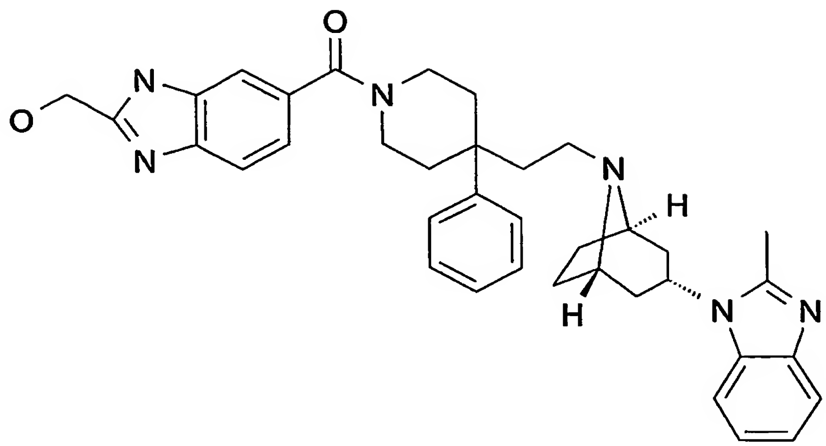
Example 959

1-[(1R,5S)-8-(2-{1-[(3-chloro-5-methylisoxazol-4-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



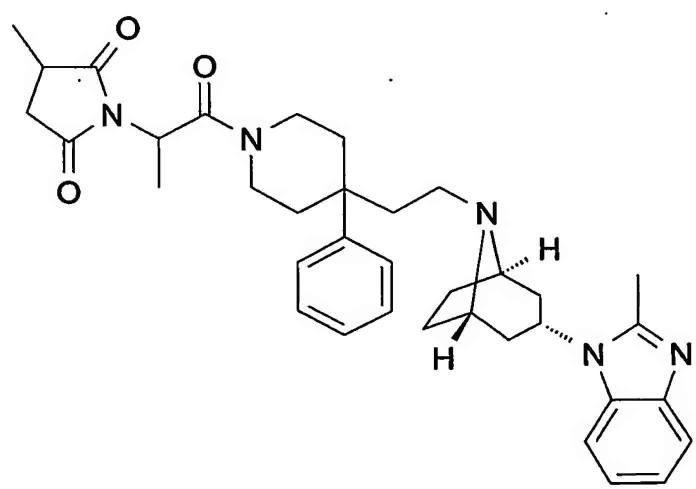
Example 960

{6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-benzimidazol-2-yl}methanol



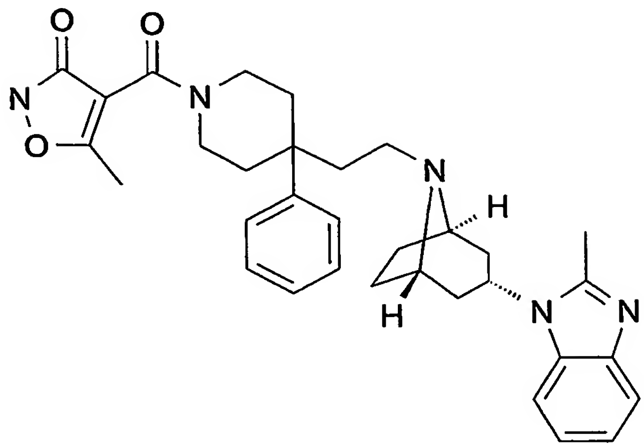
Example 961

3-methyl-1-[1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]pyrrolidine-2,5-dione



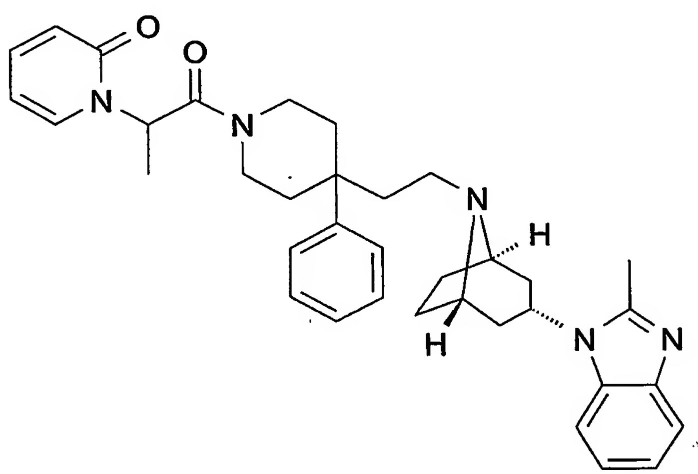
Example 962

5-methyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]isoxazol-3(2H)-one



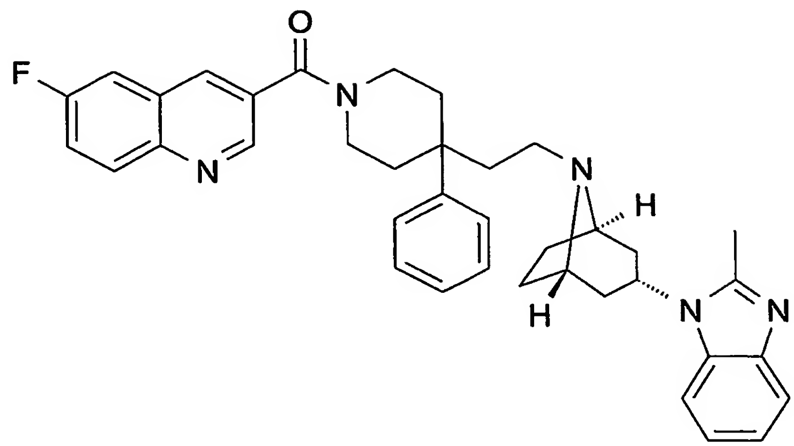
Example 963

1-[1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]pyridin-2(1H)-one



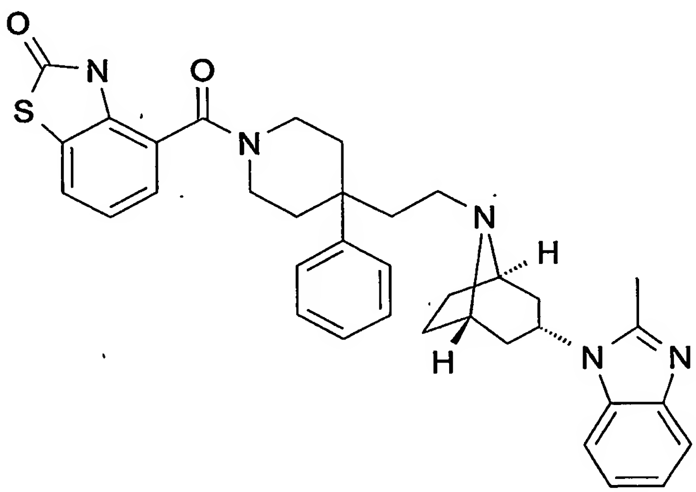
Example 964

6-fluoro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinoline



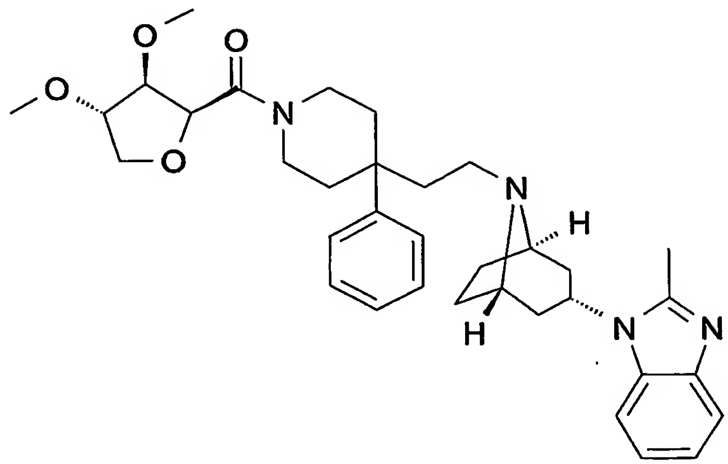
Example 965

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzothiazol-2(3H)-one



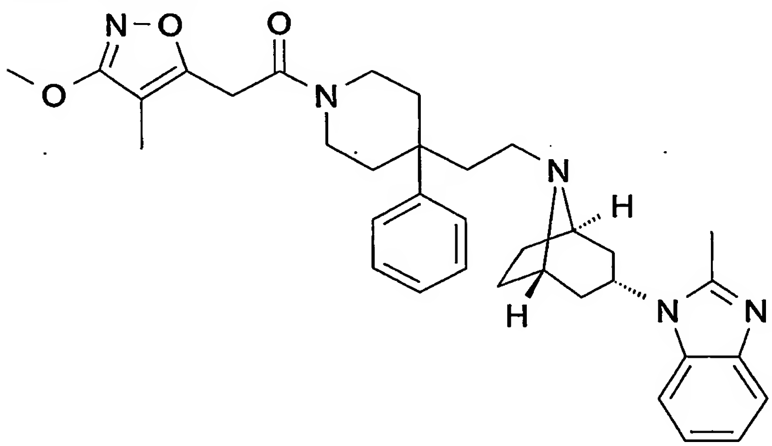
Example 966

1-((1R,5S)-8-{2-[1-((3S,4S)-3,4-dimethoxy-(2S)-tetrahydrofuran-2-carbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



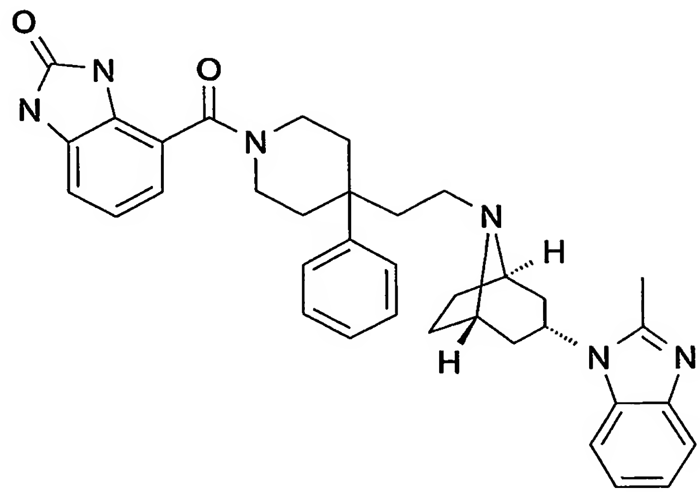
Example 967

1-[(1R,5S)-8-(2-{1-[(3-methoxy-4-methylisoxazol-5-yl)acetyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



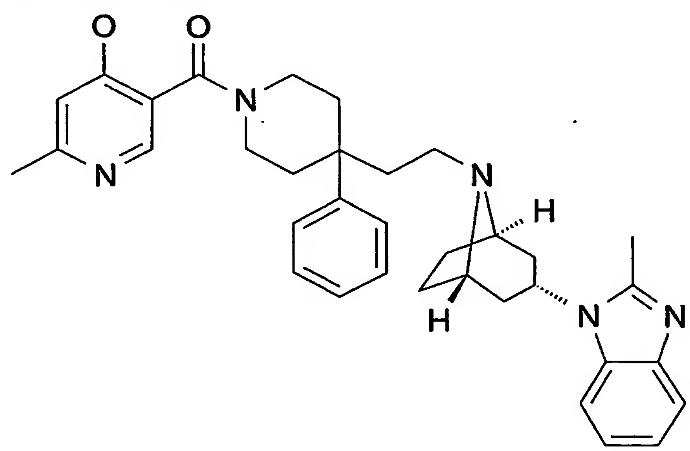
Example 968

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-dihydro-2H-benzimidazol-2-one



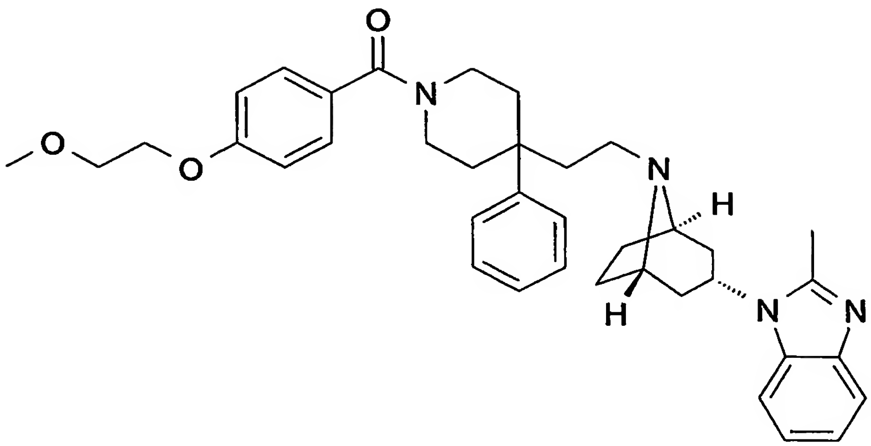
Example 969

2-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-4-ol



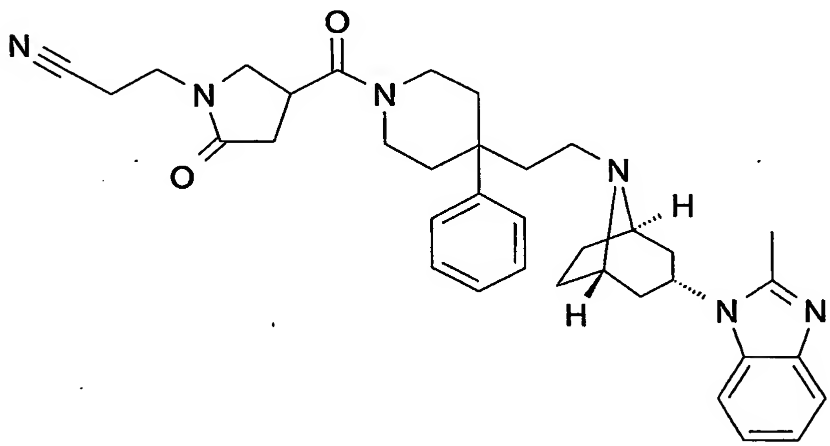
Example 970

1-[(1R,5S)-8-(2-{1-[4-(2-methoxyethoxy)benzoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



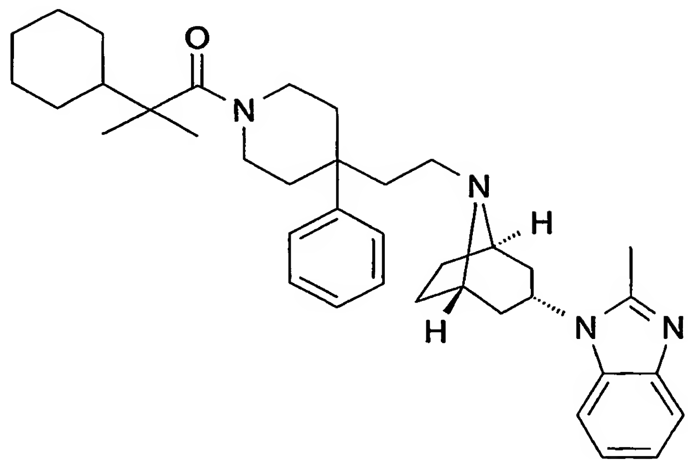
Example 971

3-{4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-2-oxopyrrolidin-1-yl}propanenitrile



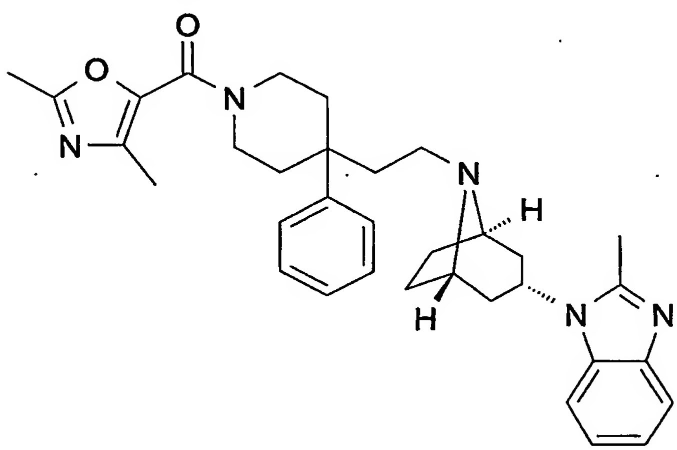
Example 972

1-((1R,5S)-8-{2-[1-(2-cyclohexyl-2-methylpropanoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



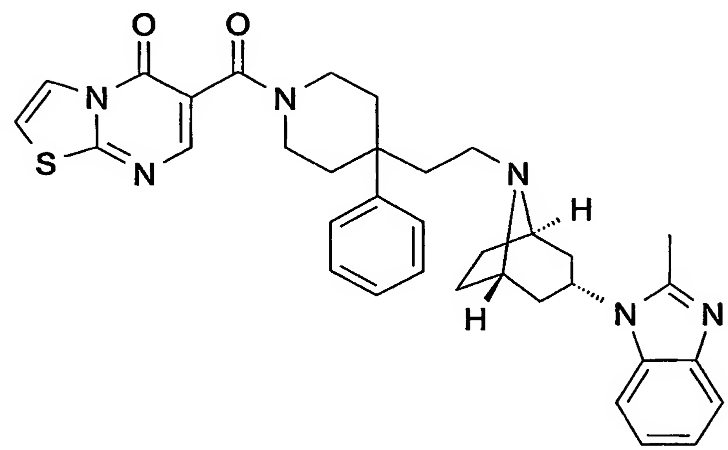
Example 973

1-[(1R,5S)-8-(2-{1-[(2,4-dimethyl-1,3-oxazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



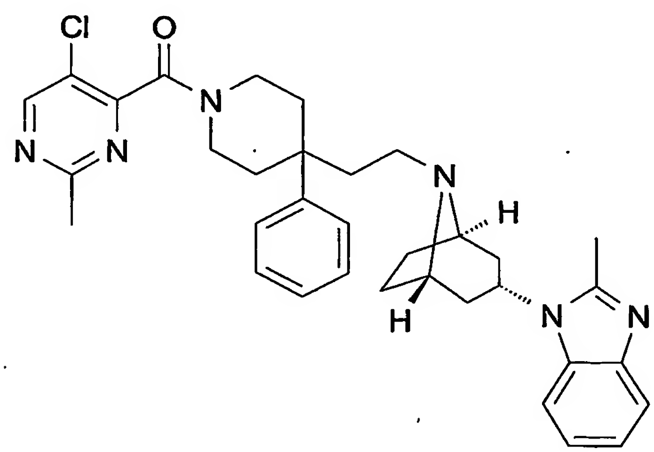
Example 974

6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one



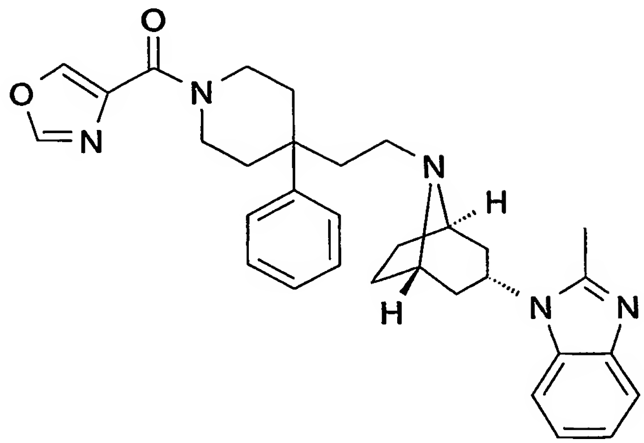
Example 975

1-[(1R,5S)-8-(2-{1-[(5-chloro-2-methylpyrimidin-4-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



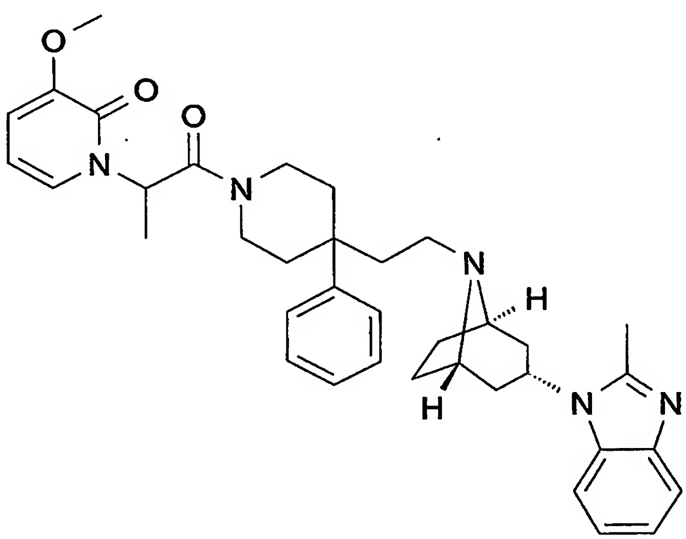
Example 976

2-methyl-1-((1R,5S)-8-{2-[1-(1,3-oxazol-4-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



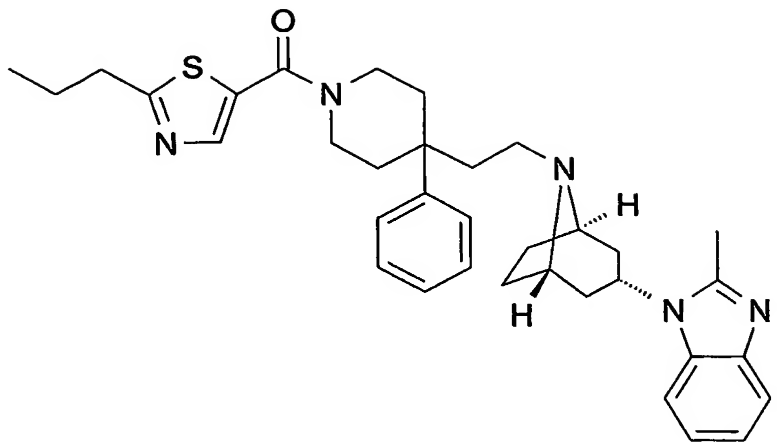
Example 977

3-methoxy-1-[1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]pyridin-2(1H)-one



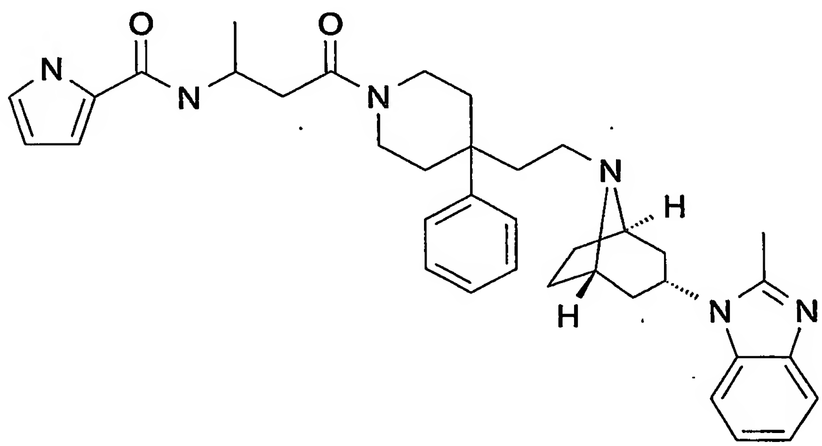
Example 978

2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(2-propyl-1,3-thiazol-5-yl)carbonyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



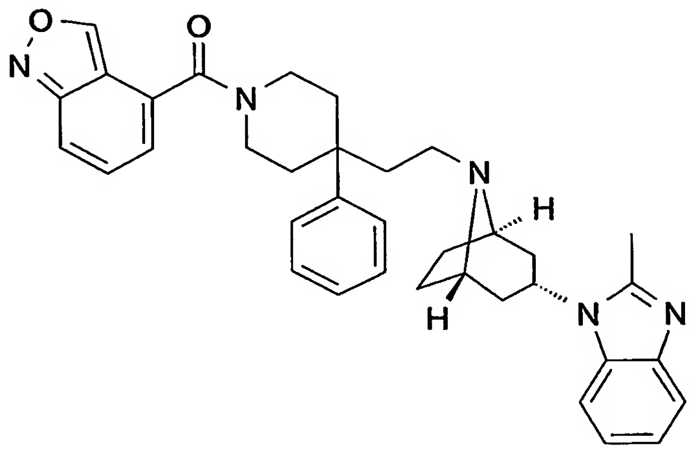
Example 979

N-[1-methyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-3-oxopropyl]-1H-pyrrole-2-carboxamide



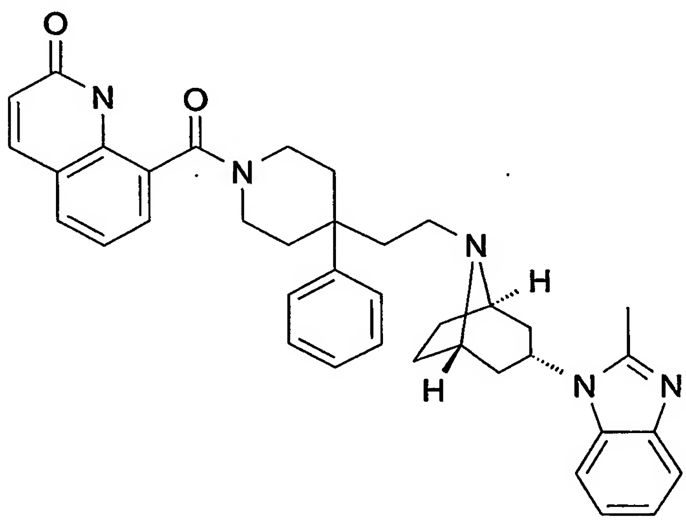
Example 980

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-2,1-benzisoxazole



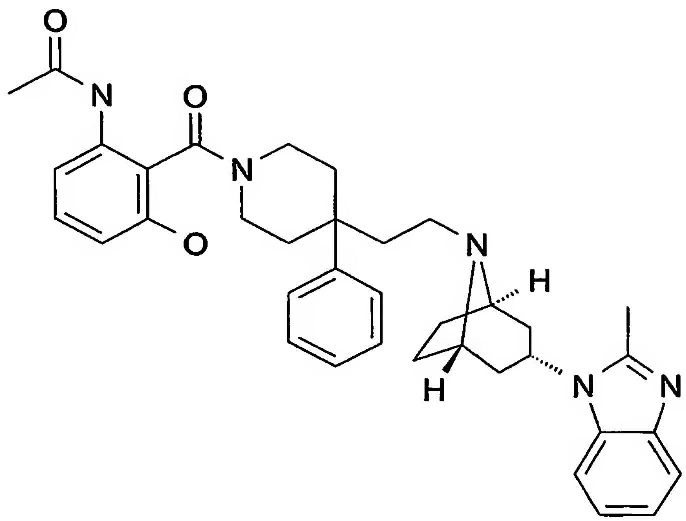
Example 981

8-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinolin-2(1H)-one



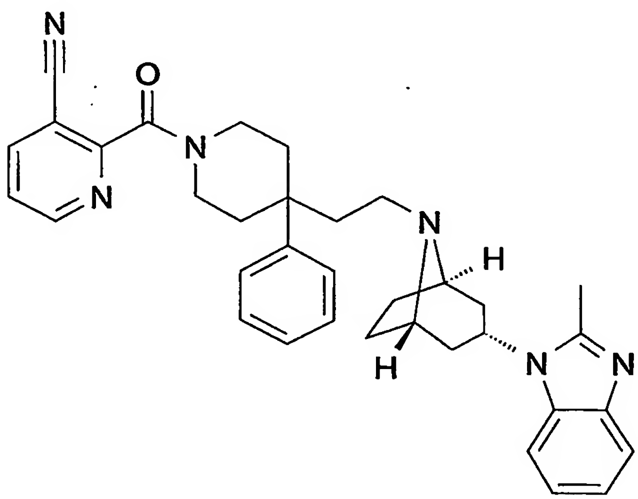
Example 982

N-{3-hydroxy-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}acetamide



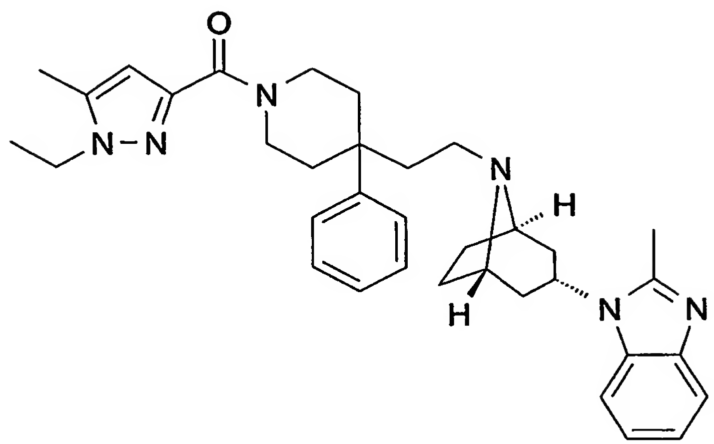
Example 983

2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinonitrile



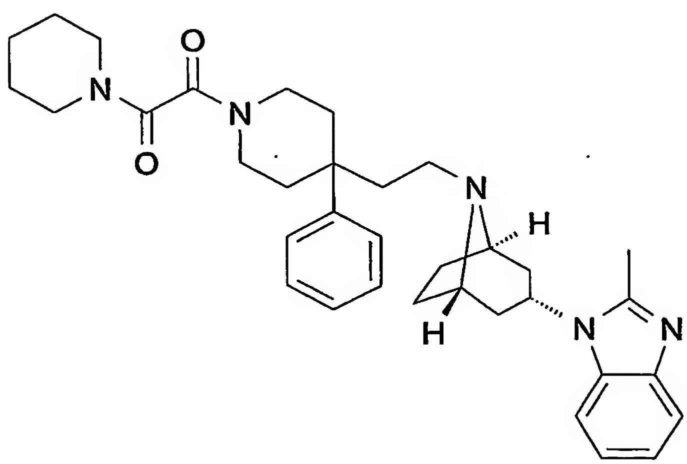
Example 984

1-[(1R,5S)-8-(2-{1-[(1-ethyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



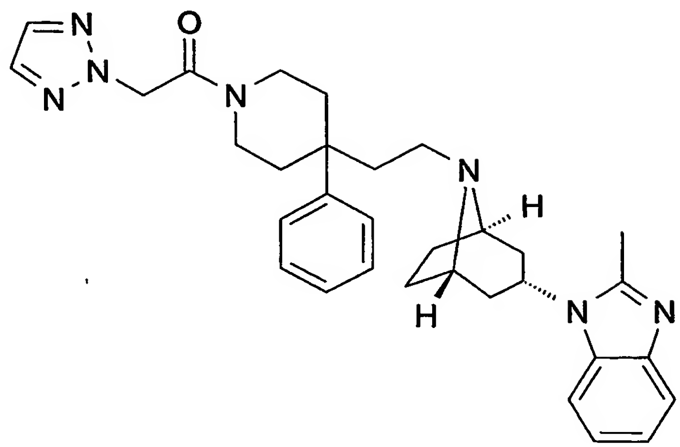
Example 985

2-methyl-1-[(1R,5S)-8-(2-{1-[oxo(piperidin-1-yl)acetyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



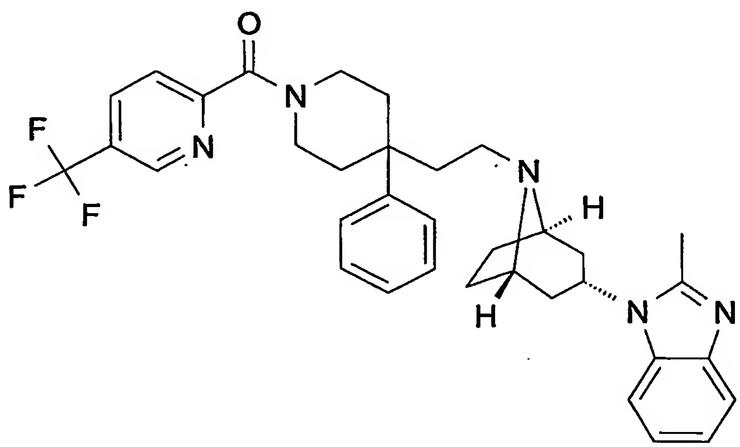
Example 986

2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(2H-1,2,3-triazol-2-ylacetyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



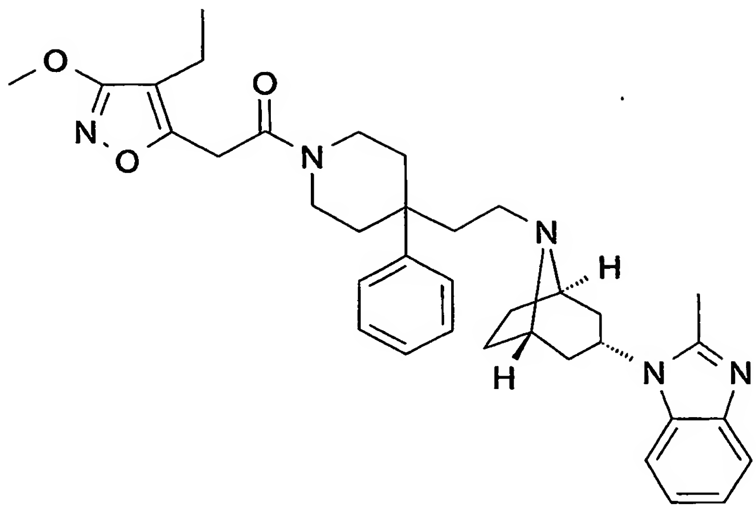
Example 987

2-methyl-1-{(1R,5S)-8-[2-(4-phenyl-1-{[5-(trifluoromethyl)pyridin-2-yl]carbonyl}piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



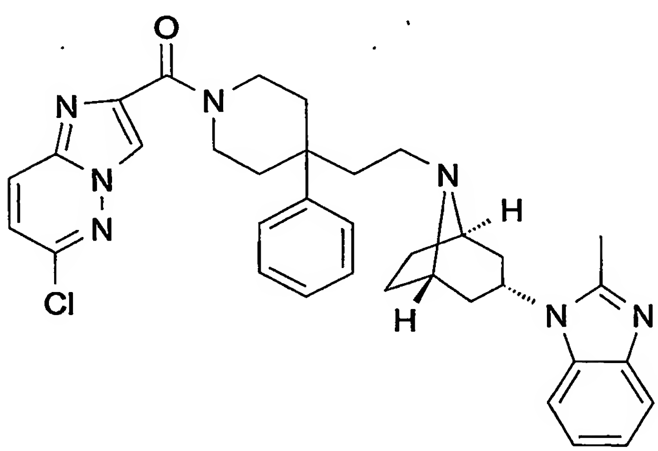
Example 988

1-[(1R,5S)-8-(2-{1-[(4-ethyl-3-methoxyisoxazol-5-yl)acetyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



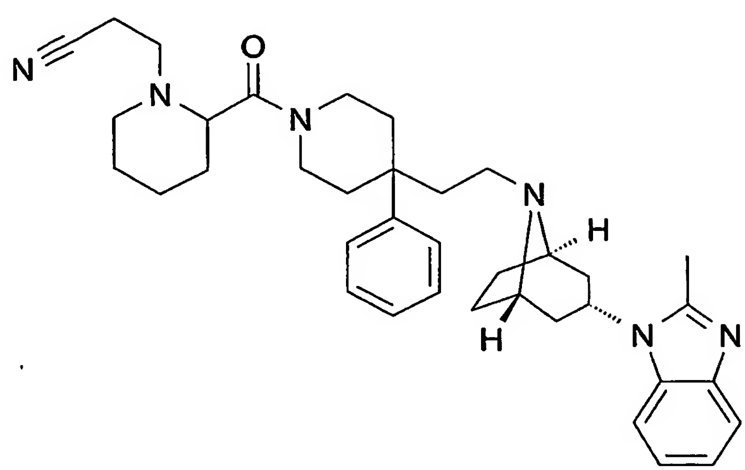
Example 989

6-chloro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]imidazo[1,2-b]pyridazine



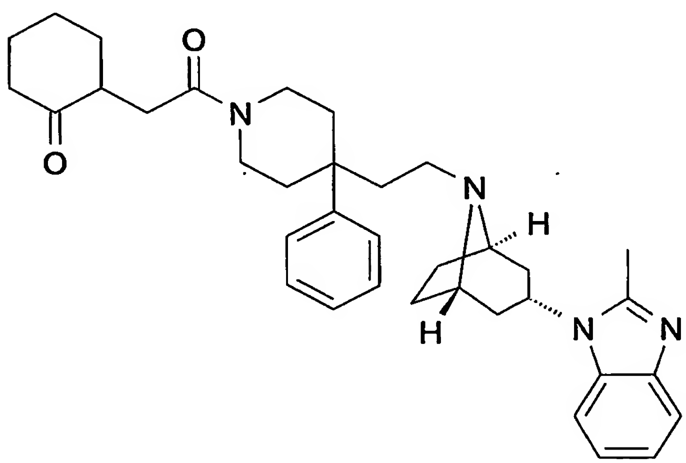
Example 990

3-{2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]piperidin-1-yl}propanenitrile



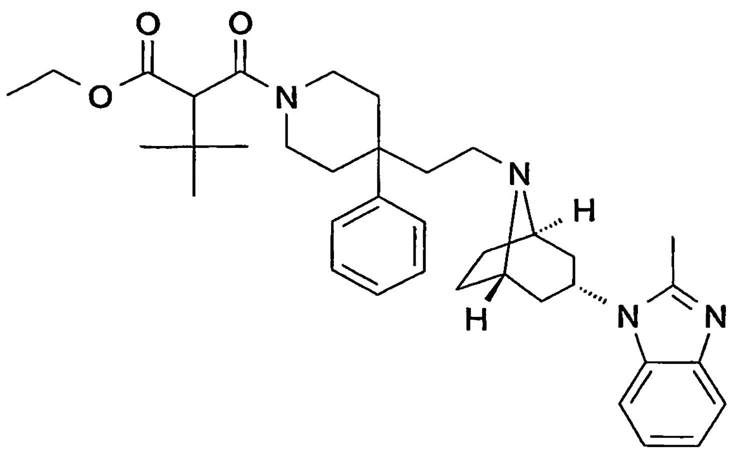
Example 991

2-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]cyclohexanone



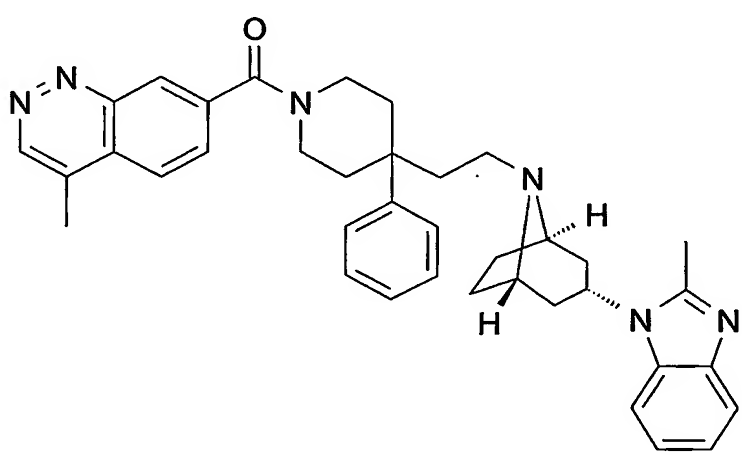
Example 992

ethyl 3,3-dimethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]butanoate



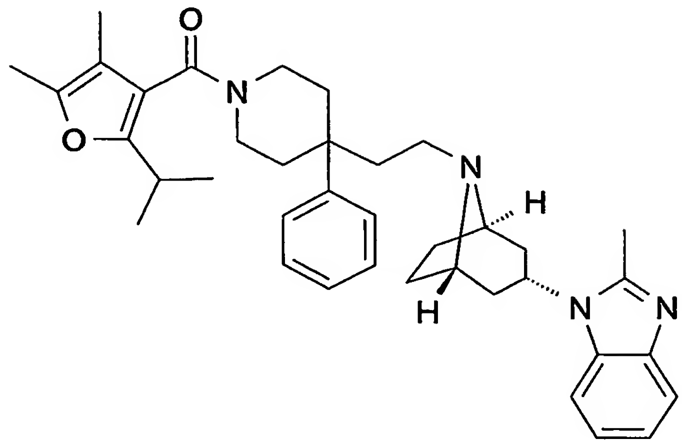
Example 993

4-methyl-7-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cinnoline



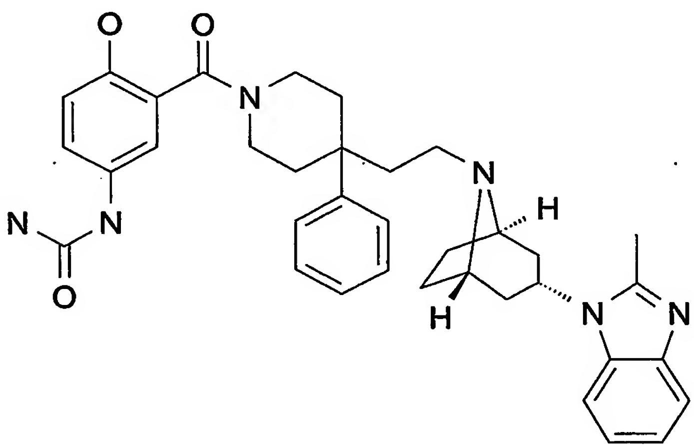
Example 994

1-((1R,5S)-8-{2-[1-(2-isopropyl-4,5-dimethyl-3-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



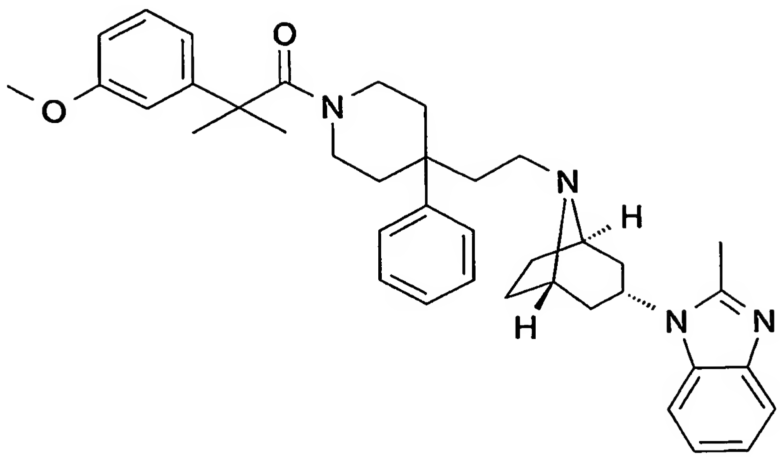
Example 995

N-{4-hydroxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}urea



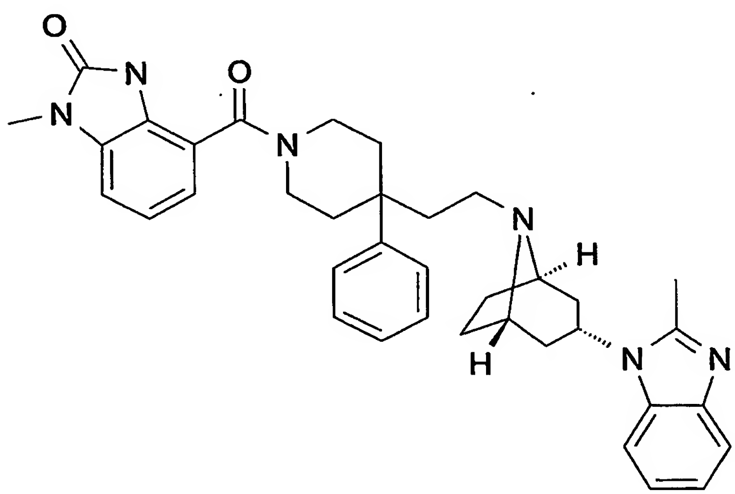
Example 996

1-[(1R,5S)-8-(2-{1-[2-(3-methoxyphenyl)-2-methylpropanoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



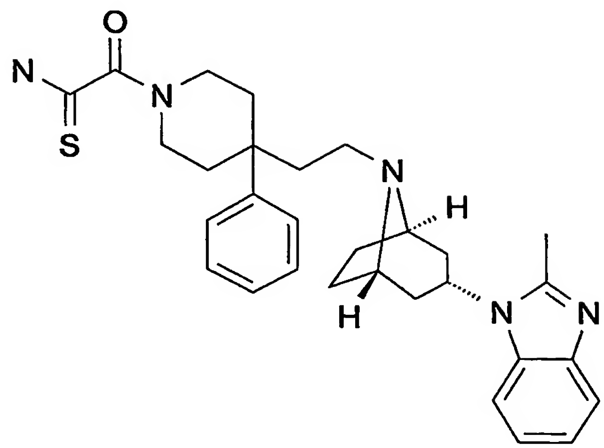
Example 997

1-methyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-dihydro-2H-benzimidazol-2-one



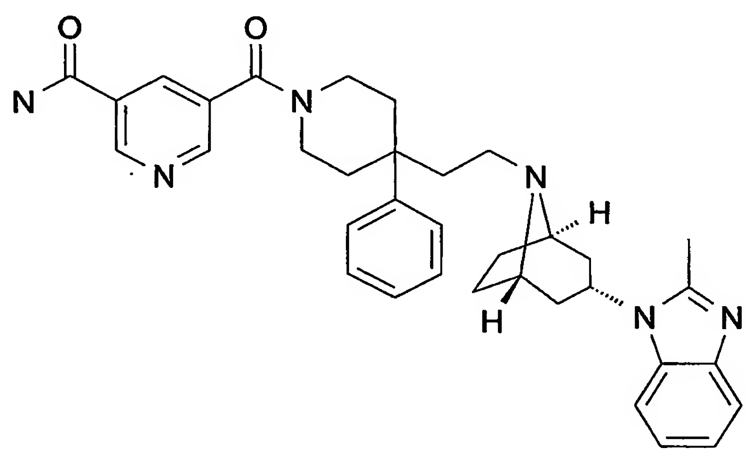
Example 998

2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethanethioamide



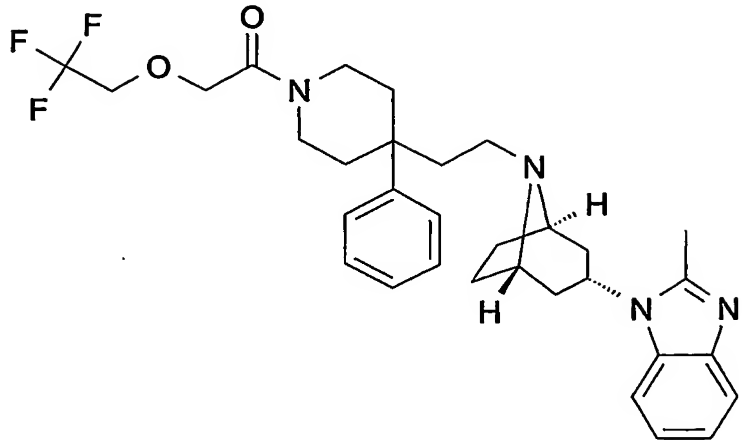
Example 999

5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinamide



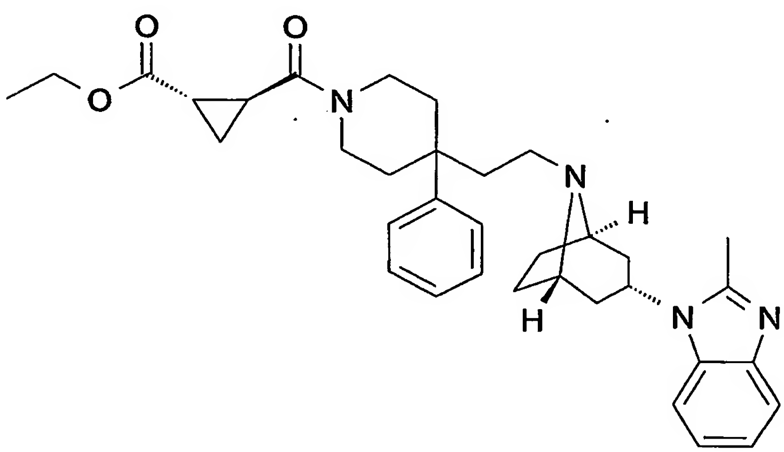
Example 1000

2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(2,2,2-trifluoroethoxy)acetyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



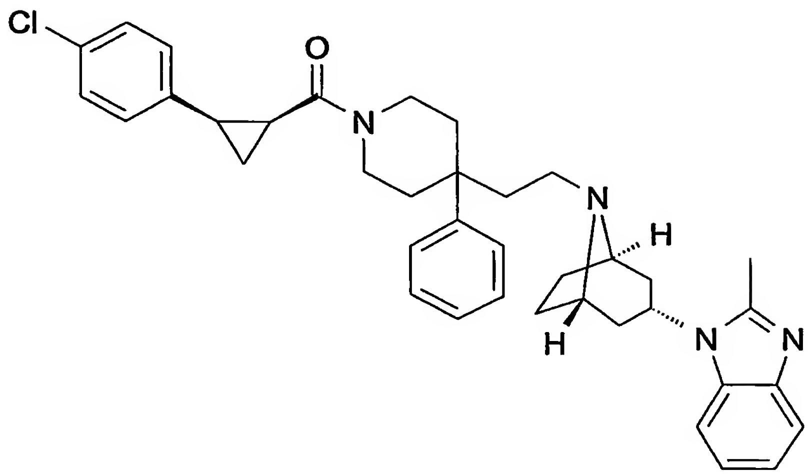
Example 1001

ethyl (1S,2S)-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclopropanecarboxylate



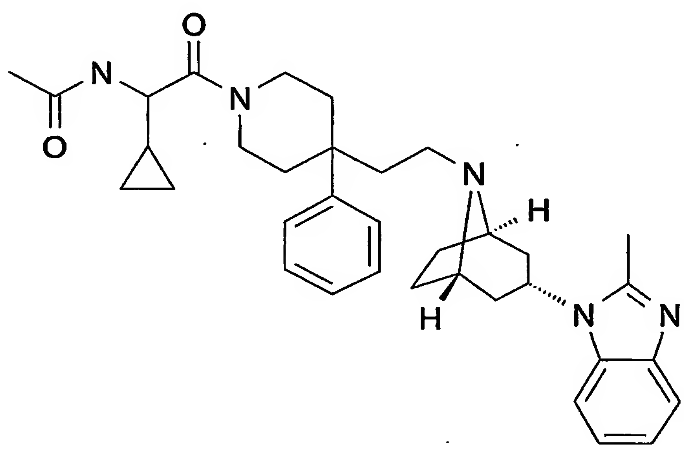
Example 1002

1-{(1R,5S)-8-[2-(1-{[(1S,2R)-2-(4-chlorophenyl)cyclopropyl]carbonyl}-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



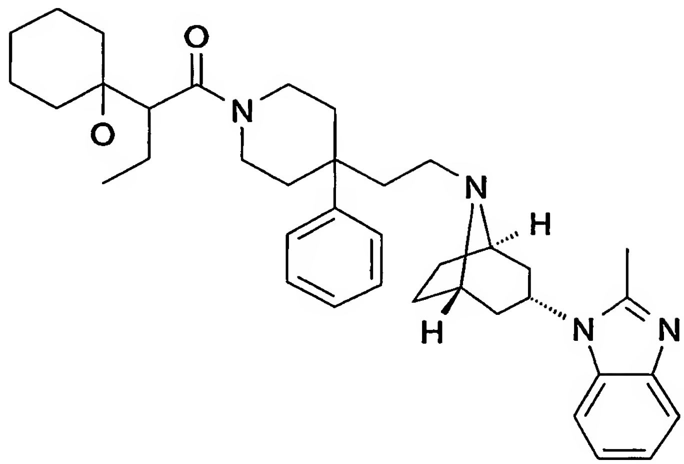
Example 1003

N-[1-cyclopropyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]acetamide



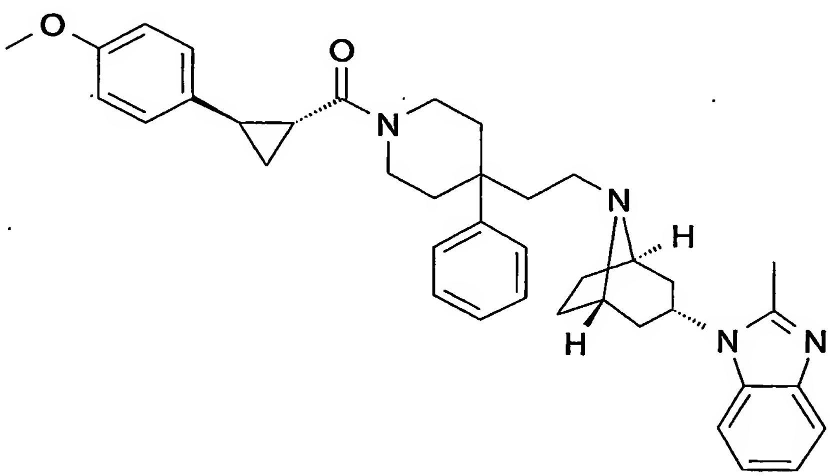
Example 1004

1-{1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]propyl}cyclohexanol



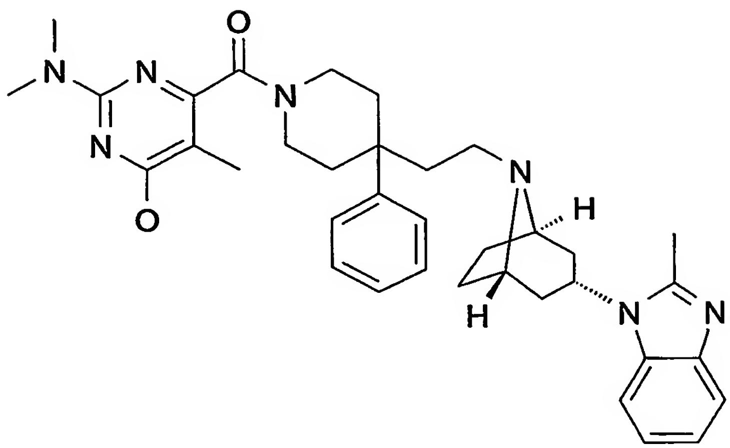
Example 1005

1-{(1R,5S)-8-[2-(1-{[(1R,2R)-2-(4-methoxyphenyl)cyclopropyl]carbonyl}-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



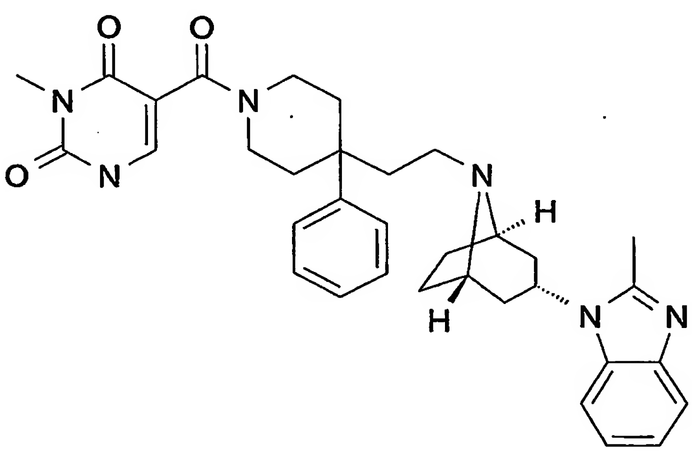
Example 1006

2-(dimethylamino)-5-methyl-6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyrimidin-4-ol



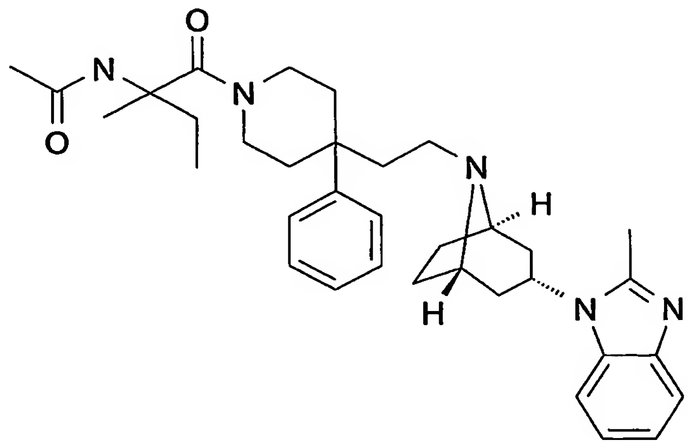
Example 1007

3-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyrimidine-2,4(1H,3H)-dione



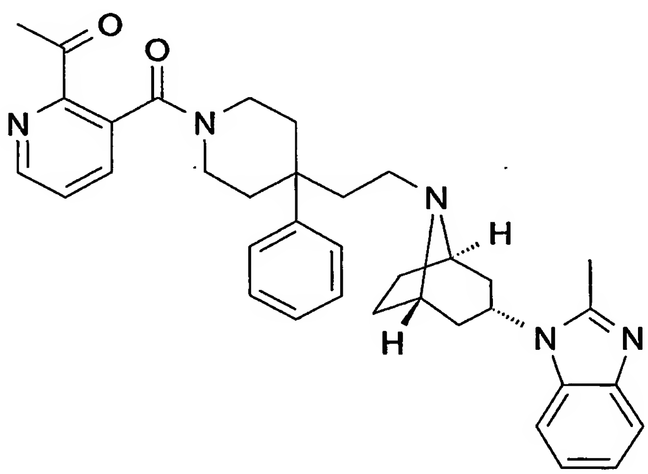
Example 1008

N-{1-methyl-1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]propyl}acetamide



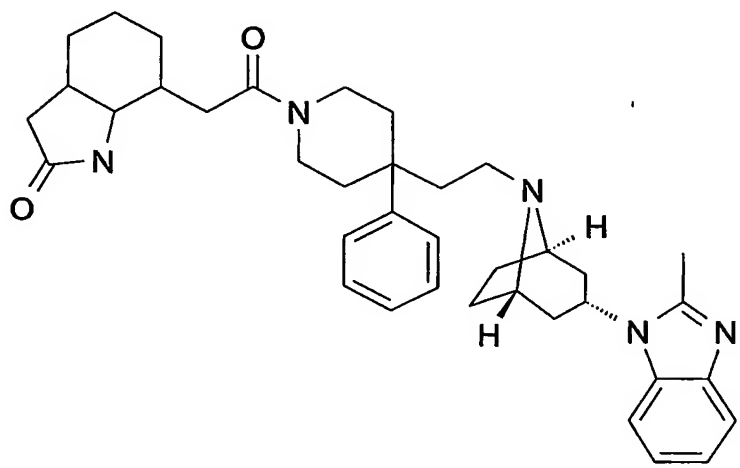
Example 1009

1-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2-yl}ethanone



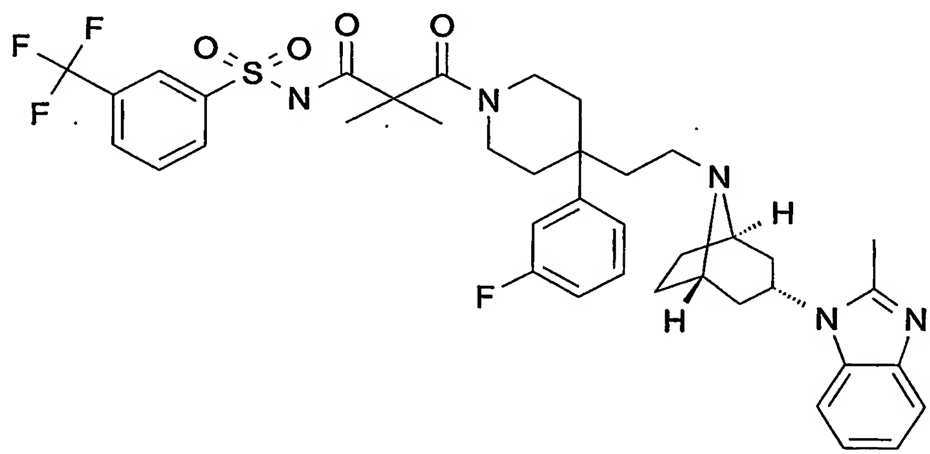
Example 1010

7-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]octahydro-2H-indol-2-one

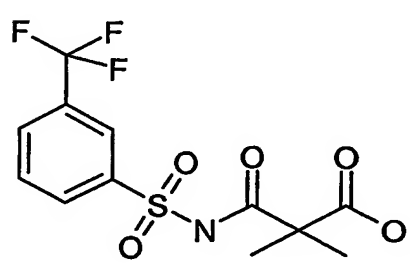


Example 1011

3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxo-N-{[3-(trifluoromethyl)phenyl]sulfonyl}propanamide



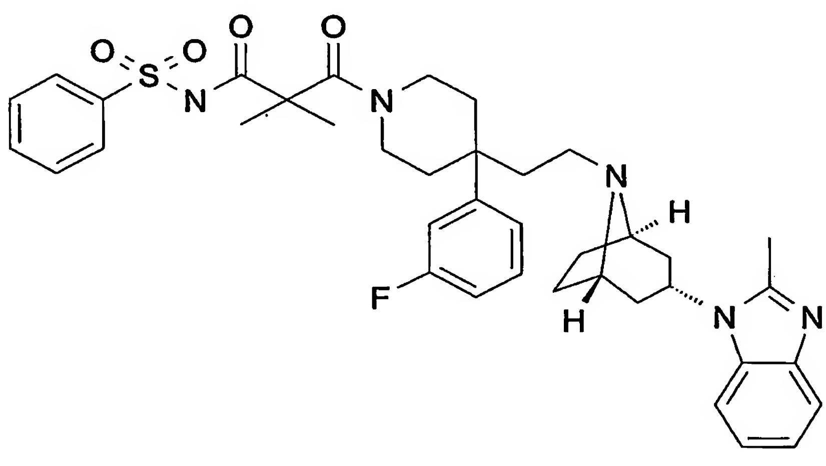
Synthesis of 2,2-dimethyl-3-oxo-3-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)propanoic acid



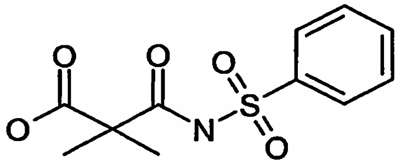
2,2-dimethyl-3-oxo-3-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)propanoic acid was prepared in the same manner as 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid starting from 3-(trifluoromethyl)benzenesulfonyl chloride.
^{1}HNMR (300MHz, Chloroform-D1) δ ppm 1.4 (m,6H) 5.1 (m,1H) 7.9 (M, 1H) 8.1 (m, 1H) 8.2 (m, 1H) 8.3 (m, 1H) 10.0 (s, 1H), Electrospray LC-MS 362 (M+23)

Example 1012

3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxo-N-(phenylsulfonyl)propanamide



The synthesis of 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid



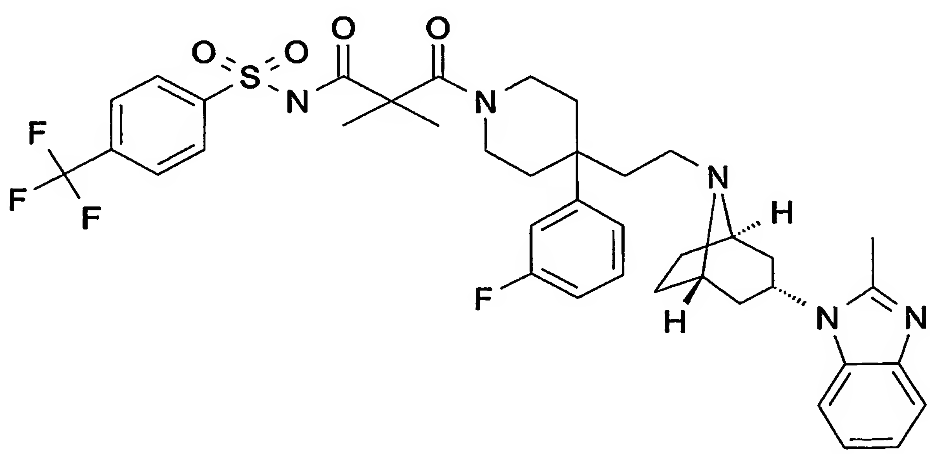
Benzenesulfonamide was made by adding benzenesulfonyl chloride to a solution of ammonia in tetrahydrofuran and evaporating to a solid. Benzenesulfonamide (87 mg, .50 mmole) was added to a shaken suspension

of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid (100 mg, .62 mmole) reactivated on PS-DCC resin (1.62 g, 1.25 mmole) and 1.50 mmole of *N,N*-dimethylpyridin-4-amine in DCE. When reaction is complete the resin is filtered off and the organic layer washed with 1N HCl dried and evaporated. The resulting resadue was disolved in 6 ml of ethanol and 6 ml of 1N LiOH was added and heated to 40 C°. The reaction was neutralized with 1N HCl and evaporated to afford 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid as a crude product which was used with no further purification.

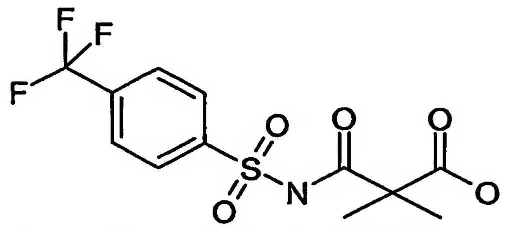
^{1}HNMR (300MHz, Chloroform-D1) δ ppm 1.4 (m, 6H) 4.9 (s, 1H) 7.6 (m, 3H) 7.9 (m, 1H) 8.1 (m, 1H) 9.8 (s, 1H), Electrospray LC-MS 180 (M+23).

Example 1013

3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxo-N-{[4-(trifluoromethyl)phenyl]sulfonyl}propanamide



The synthesis of 2,2-dimethyl-3-oxo-3-({[4-(trifluoromethyl)phenyl]sulfonyl}amino)propanoic acid

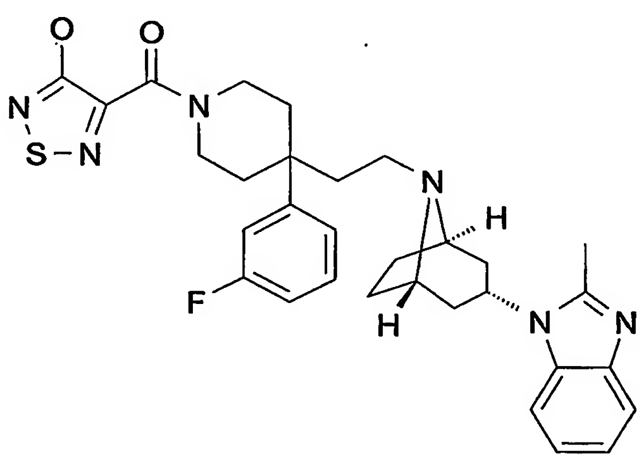


2,2-dimethyl-3-oxo-3-({[4-(trifluoromethyl)phenyl]sulfonyl}amino)propanoic acid was prepared in the same manner as 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid starting from 4-(trifluoromethyl)benzenesulfonyl chloride.

^{1}HNMR (300MHz, Chloroform-D1) δ ppm 1.4 (m,6H) 5.1 (s,1H) 7.8 (M, 2H) 8.1 (d, *J*=8.78 Hz, 1H) 8.2 (d, *J*=9.0 Hz, 1H) 9.9 (s, 1H)

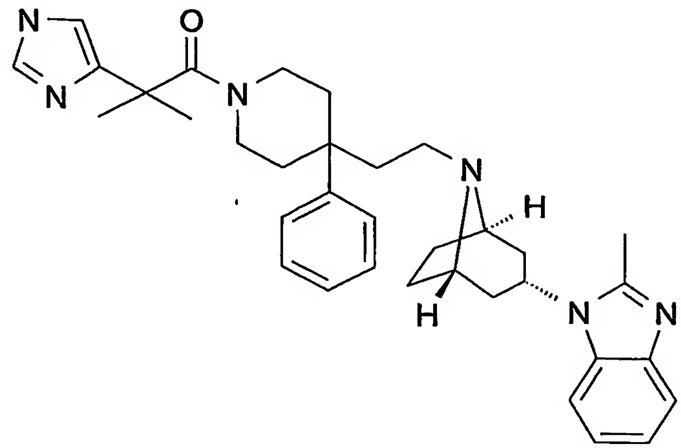
Example 1014

4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1,2,5-thiadiazol-3-ol



Example 1015

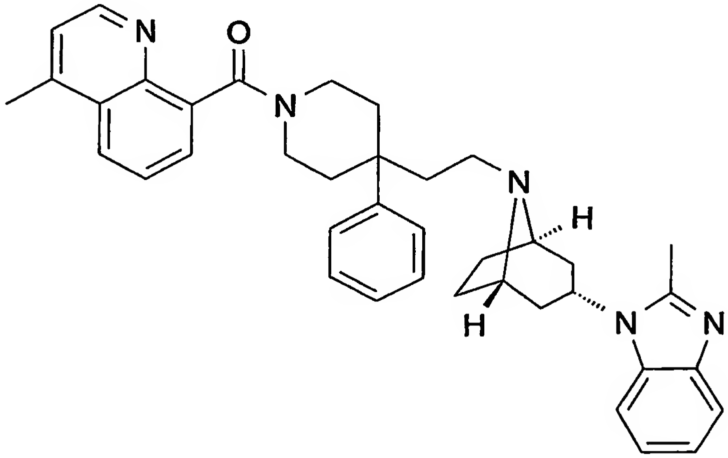
1-[(1R,5S)-8-(2-{1-[2-(1H-imidazol-4-yl)-2-methylpropanoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



Using Method A (HATU) 2-(1*H*-imidazol-4-yl)-2-methylpropanoic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 1-[(1R,5S)-8-(2-{1-[2-(1H-imidazol-4-yl)-2-methylpropanoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole 11.8 mg 42% yeild.
1H NMR (400 MHz, DMSO-D6) d ppm 1.2 (m, 1 H) 1.5 (m, 8 H) 1.7 (m, 8 H) 2.3 (m, 2 H) 2.5 (m, 3 H) 2.5 (m, 8 H) 3.2 (m, 2 H) 4.5 (m, 1 H) 7.1 (m, 10 H) 11.9 (m, 1 H)
Electrospray LC-MS 565 (M+H)

Example 1016

4-methyl-8-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinoline



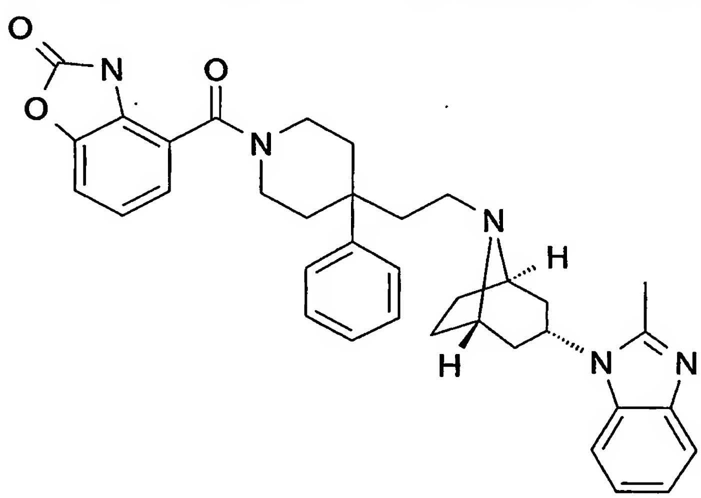
Using Method A (HATU) 4-methylquinoline-8-carboxylic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 4-methyl-8-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinoline 14.8 mg 49% yeild.

1H NMR (400 MHz, DMSO-D6) d ppm 1.7 (m, 10 H) 2.1 (m, 2 H) 2.3 (m, 6 H) 2.7 (m, 3 H) 2.9 (m, 1 H) 3.2 (m, 4 H) 3.6 (m, 1 H) 4.0 (m, 1 H) 4.5 (m, 1 H) 7.1 (m, 2 H) 7.2 (m, J=2.9 Hz, 1 H) 7.4 (m, 6 H) 7.5 (m, J=5.4 Hz, 1 H) 7.6 (m, 2 H) 8.2 (m, J=5.7, 2.1 Hz, 1 H) 8.7 (m, 1 H)

Electrospray LC-MS 598 (M+H)

<u>Example 1017</u>

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one



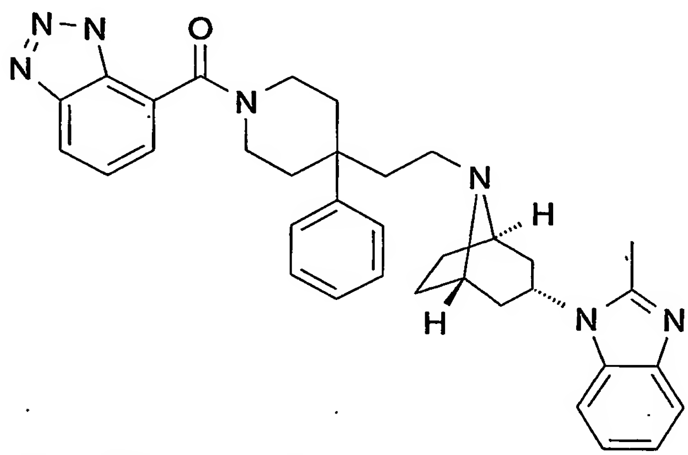
Using Method A (HATU) 2-oxo-2,3-dihydro-1,3-benzoxazole-4-carboxylic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one 8.7 mg 30% yeild.

1H NMR (400 MHz, DMSO-D6) d ppm 1.6 (m, 2 H) 1.8 (m, 9 H) 2.4 (m, 2 H) 2.4 (m, 3 H) 2.5 (m, 7 H) 3.2 (m, 3 H) 4.5 (m, 1 H) 7.2 (m, 5 H) 7.4 (m, 6 H) 7.5 (m, 1 H)

Electrospray LC-MS 590 (M+H)

Example 1018

7-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole



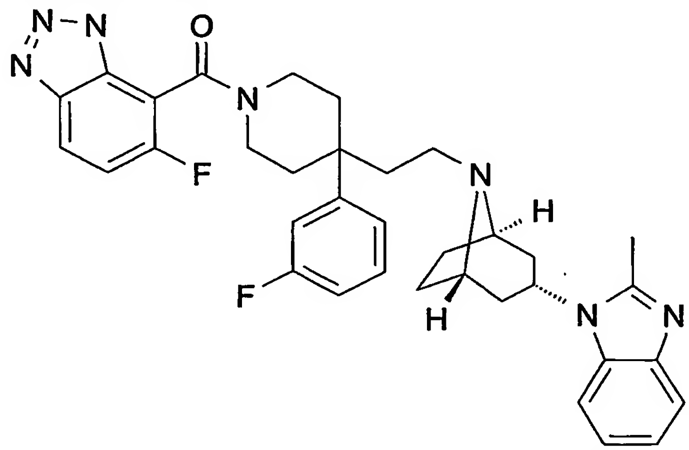
Using Method A (HATU) 1*H*-1,2,3-benzotriazole-7-carboxylic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 7-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole 9.9 mg 34% yeild.

1H NMR (400 MHz, DMSO-D6) d ppm 1.6 (m, 1 H) 1.8 (m, 8 H) 2.4 (m, 4 H) 2.5 (m, 8 H) 3.2 (m, 3 H) 4.0 (m, 1 H) 4.5 (m, 1 H) 7.1 (m, 2 H) 7.2 (m, 1 H) 7.4 (m, 8 H) 8.0 (m, 1 H)

Electrospray LC-MS 574 (M+H)

Example 1019

6-fluoro-7-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole

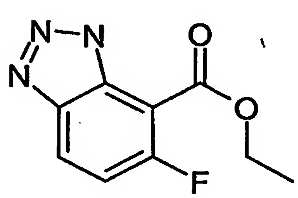


Using Method A (HATU) 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylic acid and endo-1-(8-{2-[4-(3-flourophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride were coupled to afford 6-fluoro-7-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole 83.9 mg 62% yeild.

1H NMR (400 MHz, METHANOL-D4) d ppm 1.7 (m, 1 H) 2.0 (m, 4 H) 2.4 (m, 4 H) 2.8 (m, 3 H) 3.4 (m, 13 H) 4.7 (m, 1 H) 7.2 (m, 10 H) 7.9 (m, 1 H)

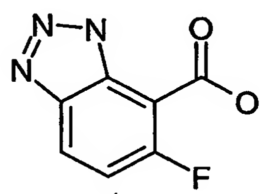
Electrospray LC-MS 610 (M+H)

Preparation of the ethyl 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylate



ethyl 2,3-diamino-6-fluorobenzoate (1.00 g, 5.04 mmole) in 50 ml of water and 10 ml acetic acid was cooled to –10 C°. To this solution was added dropwise sodium nitrite (348 mg, 5.04 mmole) in 30 ml of water. After the addition the reaction was warmed to 0 C° for 30 min, then to room temperature for 1 hr, and finally 50 C° for 1 hr. The reaction was filtered after stirring over night and washed with water. The dark brownish purple solid was disoved in ethylacetate dried over magnesium sulfate and evaporated to afford ethyl 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylate (920 mg, 87% yield)
1H NMR (400 MHz, METHANOL-D4) □ ppm 1.3 (t, *J*=7.1 Hz, 3 H) 4.4 (q, *J*=7.0 Hz, 2 H) 7.2 (dd, *J*=11.2, 9.0 Hz, 1 H) 8.1 (dd, *J*=9.1, 4.1 Hz, 1 H)

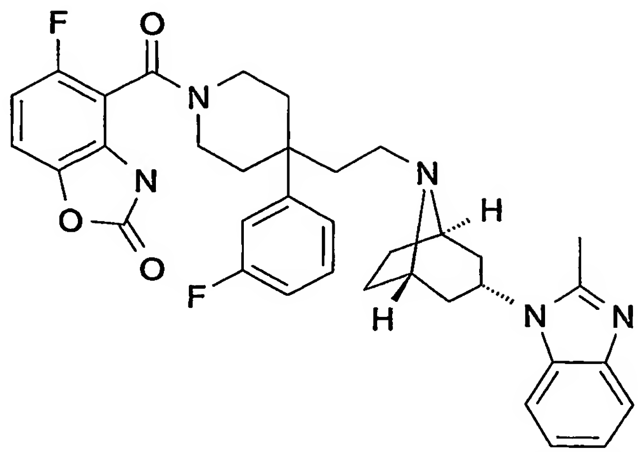
Preparation of the 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylic acid



ethyl 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylate (920 mg) was heated in 6N HCl untill all of the starting material disappeared. Evaporation of the HCl afforded 718 mg of a brownish solid.
1H NMR (300 MHz, DMSO-D6) □ ppm 7.4 (dd, *J*=11.2, 9.0 Hz, 1 H) 8.3 (dd, *J*=9.1, 4.1 Hz, 1 H)

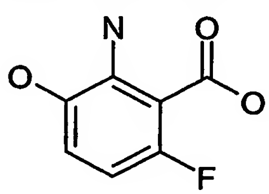
<u>Example 1020</u>

5-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one



Using Method A (HATU) 5-fluoro-2-oxo-2,3-dihydro-1,3-benzoxazole-4-carboxylic acid and endo-1-(8-{2-[4-(3-flourophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride were coupled to afford 5-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one. 1H NMR (300 MHz, METHANOL-D4) d ppm 1.4 (d, J=6.5 Hz, 1 H) 1.8 (m, 3 H) 2.0 (m, 8 H) 2.2 (m, 3 H) 2.5 (m, 3 H) 3.0 (m, 3 H) 3.5 (m, 4 H) 4.2 (m, 1 H) 7.0 (m, 2 H) 7.3 (m, 7 H) 7.6 (m, 1 H) 8.0 (m, 1 H) Electrospray LC-MS 626(M+H)

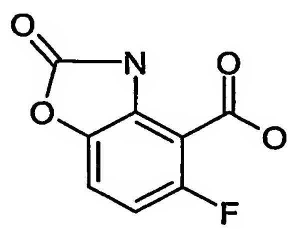
Preparation of
2-amino-6-fluoro-3-hydroxybenzoic acid



2-amino-6-fluorobenzoic acid (5.00 g, 32.2 mmole) was dissolved in 30 ml of 2N sodium hydroxide. To this was added dropwise a solution of sodium persulfate (7.67 g, 32.2 mmole) in 80 ml of water. After stirring over night the resulting black solution was extracted with 2 L of ether and 1 L of ethylacetate. Evaporation of the water gave a black solid that was used with no purification.

1H NMR (400 MHz, DMSO-D6) □ ppm 6.2 (dd, *J*=11.5, 8.6 Hz, 1 H) 6.7 (dd, *J*=8.6, 4.9 Hz, 1 H)
LC-MS

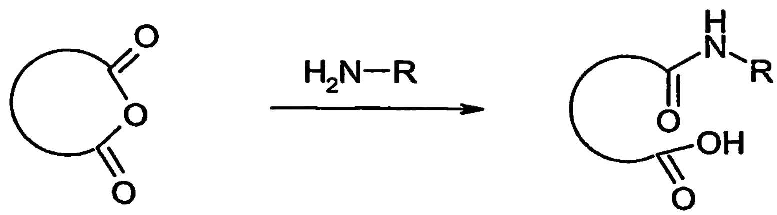
5-fluoro-2-oxo-2,3-dihydro-1,3-benzoxazole-4-carboxylic acid



To a THF solution of 2-amino-6-fluoro-3-hydroxybenzoic acid (520 mg, 3.04 mmole) and n,n-diisopropylethylamine (942 mg, 7.29 mmole) was added bis(trichloromethyl) carbonate (1.08 g, 3.64 mmole) and stirred. Removal of solvent under vacuum afforded a residue, which was run on reversephase flash chromatography 10 to 90% acetonitrile water (0.01% TFA). The resulting fractions were evaporated.
APCI LC-MS 196 (M-H) 198 (M+H)

Examples below were synthesized as follows.

Method AA. Synthesis of functionalized carboxamide carboxylic acids via amination of cyclic anhydrides (Acids 69-79 and 97-153).
1mmol of anhydride was treated with 10mmol of either a 0.5M solution of NH3 in Dioxane or a 2M solution of either methylamine, ethylamine, isopropylamine or cyclopropylamine in THF at 40°C in a sealed tube for 72h. The reaction mixtures were concentrated to remove solvent and excess amine to give the crude carboxamide carboxylic acid as the salt of the corresponding amine. Crude materials were used without further purification or characterization in the subsequent coupling reaction to generate final compounds.



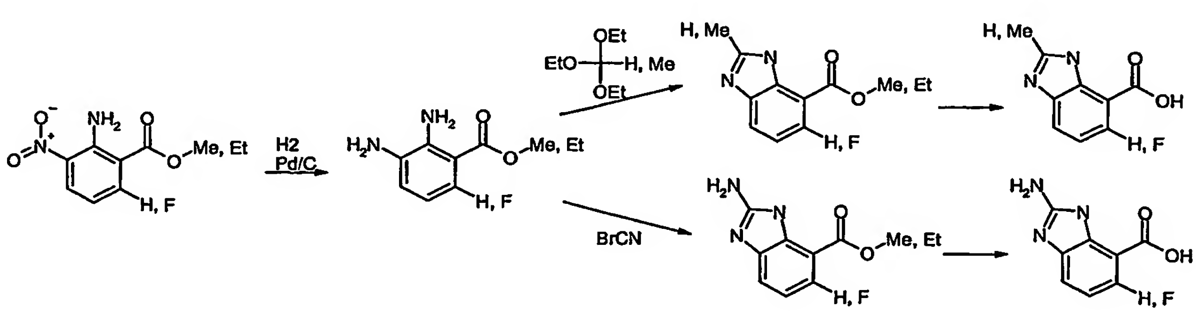
Method BB. Synthesis of benzimidazole carboxylic acids (Acids 65-68, 88, and 89)

Step 1: 50mmol of an appropriately substituted 2-amino-3-nitrobenzoic acid ester in 250mL of EtOH/EtOAc (1:1) was treated with 980mg of 10%Pd/C and H2(g) (1atm) at ambient temperature for 16h. The catalyst was filtered off and the filtrate concentrated to give the corresponding dianiline as a crystaline solid in quantitative yield. The crude material was carried on to either step 2A or 2B without further purification.

Step 2A: 5.6mmol of the dianiline was treated with 15mL of either triethyl orthoacetate or triethyl orthoformate at 120°C for 16h. The reaction mixture was concentrated to dryness to give the corresponding benzimidazole as a crystaline solid that was carried on to step 3 without further purification.

Step2B: Alternatively, 6.0mmol of dianiline was treated with 6.3mmol BrCN in 15mL CH3OH at reflux for 3h. The reaction mixture was cooled to ambient temperature and precipitate was filtered off to give the corresponding 2-aminobenzimidazole.

Step 3: Benzimidazoles obtained from steps 2A and 2B were treated with 6N HCl at 80°C for 8h. The reaction mixtures were concentrated to dryness to give the benzimidazole carboxylic acids which were used without purification in coupling reactions to yield final compounds.

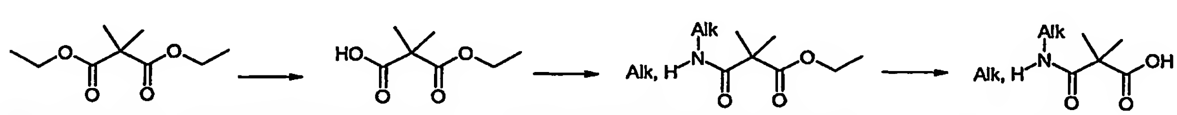


Method CC. Synthesis of carboxamide carboxylic acids by amination of dimethyl malonate (Acids 90-96).

Step 1: Diethyl dimethylpropanedioate (10g, 53mmol) in 170mL EtOH was treated with 3.00g (53mmol) KOH at ambient temperature for 4 days. The reaction mixture was concentrated to dryness and partitioned between EtOAc and water. The aqueous phase was isolated, combined with fresh EtOAc and the pH adj to 2 with 6N HCl. The organic phase was isolated and the aqueous portion extracted twice with EtOAc. The organic phases were combined, dried over MgSO4, filtered and concentrated to give 6.56g (41mmol) 3-(ethyloxy)-2,2-dimethyl-3-oxopropanoic acid as a clear oil. 1H NMR (300 MHz, CDCl3) d 4.20 (q, *J*=7.1Hz, 2H), 1.46(s, 6H), 1.26(t, *J*=7.1Hz, 3H).

Step 2: 400mg (2.50mmol)) 3-(ethyloxy)-2,2-dimethyl-3-oxopropanoic acid dissolved in 4mL THF was treated with 1,1'-carbonyldiimidazole (405mg, 2.50mmol) at ambient temperature until CO2 evolution ceased (~20min). To this solution was added 7.50mmol (3eq) of either ammonia, methylamine, ethylamine, 2-amino-2-methyl-1-propanol, cyclopropylamine, isopropylamine, 2-propen-1-ylamine, or N,N-dimethylamine. The reaction mixtures were shaken gently at ambient temperature for 16h, concentrated to dryness, partitioned between DCE (8mL) and 0.5N HCl (10mL), shaken vigorously , organic phases isolated, dried over MgSO4 filtered and concentrated to dryness. Identity of these carboxamide ester intermediates was confirmed by 1H NMR.

Step 3: The carboxamide esters so obtained were treated with 2.5mL (2.5mmol) of 1N LiOH in 2.5mL EtOH at ambient temperature for 16h. The reaction mixtures were concentrated to dryness and used in coupling reations without further purification or characterization.



Method DD: Synthesis of carboxamide carboxylic acids from iodobenzoic acids or ester carboxylic acids (Acids 80-86) as exemplified by synthesis of 3-

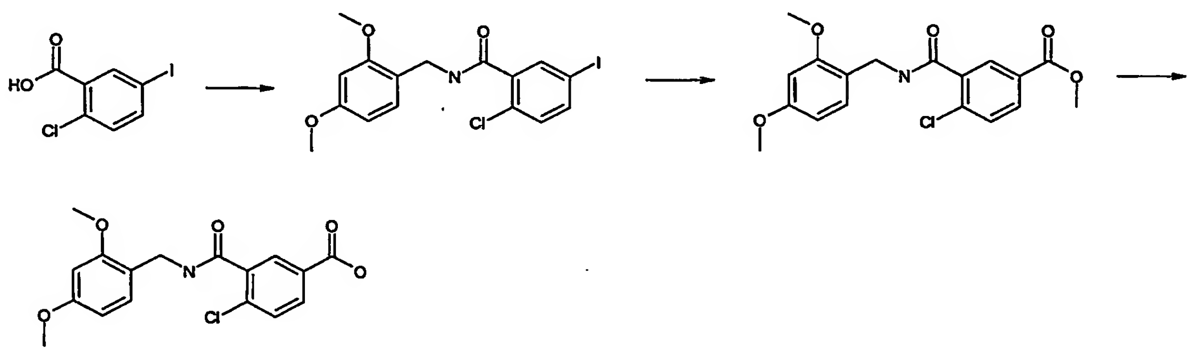
[({[2,4-bis(methyloxy)phenyl]methyl}amino)carbonyl]-4-chlorobenzoic acid (Acid 84).

Step 1: 2-Chloro-5-iodobenzoic acid (2g , 7.08mmol) in 25mL THF was treated with 1,1'-carbonyldiimidazole (1.15g , 7.08mmol) at ambient temperature until CO2 evolution ceased (~20min). 2,4-Dimethoxybenzylamine (1.18g, 7.08mmol) was added and stirred at ambient temperature for 16h. The reaction mixture was concentrated to dryness, partitioned between EtOAc and saturated NaHCO3, the organic phase isolated, dried over MgSO4, filtered and concentrated to give *N*-{[2,4-bis(methyloxy)phenyl]methyl}-2-chloro-5-iodobenzamide (3.00g, 6.95mmol) as a pale yellow oil that crystallized on standing. 1H NMR (300 MHz, CDCl3) d 7.95(d, *J*=2.2Hz, 1H), 7.62(dd, *J*=8.5, 2.2Hz, 1H), 7.25(m, 1H), 7.10 (m, 1H), 6.63(m, 1H), 6.45 (m, 2H), 4.55(d, *J*=5.7 Hz, 2H), 3.83(s, 3H), 3.80(s, 3H). LCMS ES+ 431.82, 433.77 (M+H).

Step 2: *N*-{[2,4-bis(methyloxy)phenyl]methyl}-2-chloro-5-iodobenzamide (2.78g, 6.44mmol) dissolved in 100mL CH3OH with dicyclohexylamine (3.85mL, 19mmol) was treated with POPd2 catalyst (AC2000) under an atmosphere of CO(g) at 1atm pressure and ambient temperature for 3 days. The catalyst was filtered off and the filtrate concentrated to a small volume, cooled in ice bath, and the resultant precipitate filtered off. A second crop was obtained from the mother liquor and the two batches were combined to give methyl 3-[({[2,4-bis(methyloxy)phenyl]methyl}amino)carbonyl]-4-chlorobenzoate (2.26g, 6.21mmol) as a white crystaline solid. 1H NMR (300 MHz, DMSO-D6) d 8.82(m, 1H), 7.96(dd, *J*=8.3, 2.2Hz, 1H), 7.91(m, 1H), 7.65(d, *J*=8.3Hz, 1H), 7.19(d, *J*=8.2Hz, 1H), 6.56 (d, *J*=2.5Hz, 1H), 6.51(dd, *J*=8.3, 2.5Hz, 1H), 4.34(d, *J*=5.9Hz, 2H), 3.86(s, 3H), 3.79(s, 3H), 3.74(s, 3H). LCMS ES+ 363.99, 365.97(M+H).

Step 3: Methyl 3-[({[2,4-bis(methyloxy)phenyl]methyl}amino)carbonyl]-4-chlorobenzoate (600mg, 1.65mmol) dissolved in 17mL CH3OH was treated with 16.5mL 1N LiOH at ambient temperature for 16h. The reaction mixture was concentrated to dryness, partitioned between EtOAc and water, the aqueous phase isolated and the pH adjusted to 2 with 6N HCl. The resultant

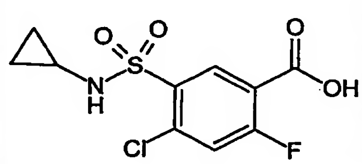
precipitate was cooled in an ice bath with stirring, filtered, and washed with water to give 3-[({[2,4-bis(methyloxy)phenyl]methyl}amino)carbonyl]-4-chlorobenzoic acid (533mg, 1.52mmol) as a white crystaline solid. 1H NMR (300 MHz, DMSO-D6) d ppm 8.96(m, 1H), 8.29(d, *J*=2.2 Hz, 1 H), 8.00(dd, *J*=8.4, 2.3 Hz, 1 H), 7.65(d, *J*=8.3 Hz, 1 H), 7.09(d, *J*=8.3 Hz, 1 H), 6.55(d, *J*=2.3 Hz, 1 H), 6.50(dd, *J*=8.3, 2.3 Hz, 1 H), 4.35(d, *J*=5.6 Hz, 1 H), 3.79(s, 3H), 3.73(s, 3H). LCMS ES+ 349.88, 351.91 (M+H).

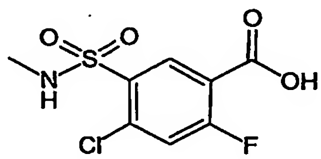
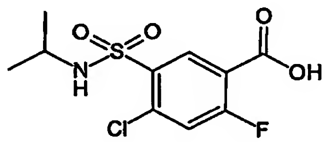
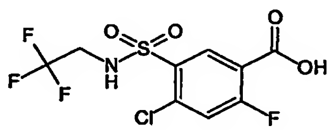
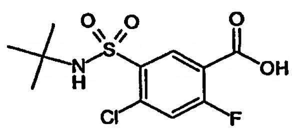
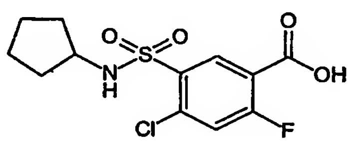
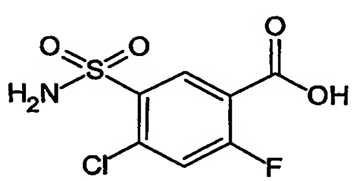
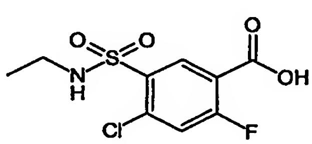
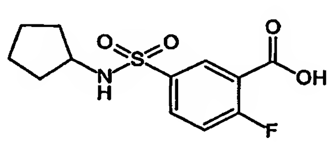


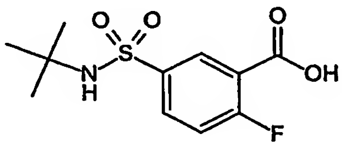
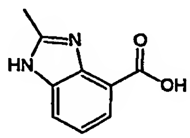
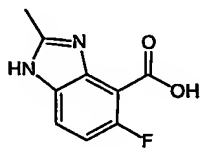
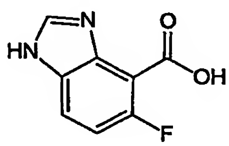
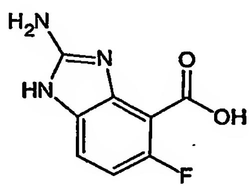
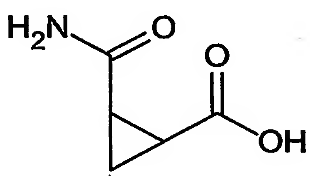
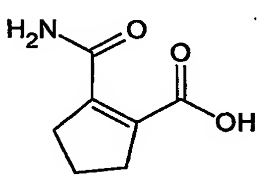
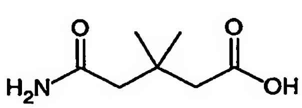
Acids 80-83 were synthesized in an analogous fashion from the appropriately substituted iodobenzoic acid and the appropriate amine.

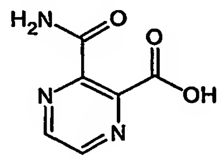
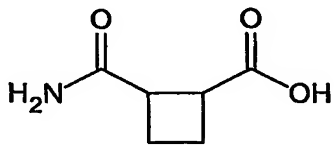
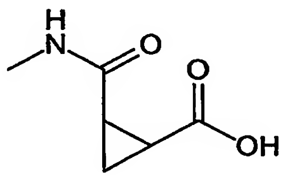
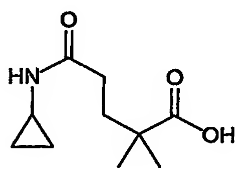
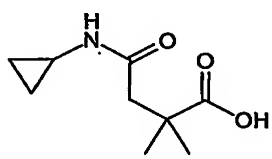
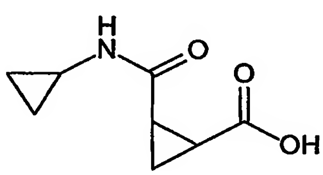
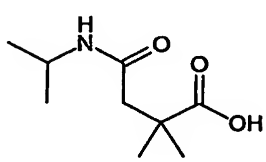
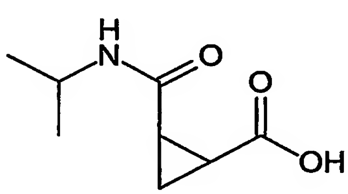
Acids 85, 86, and 154 were synthesized from diethyl dimethylpropanedioate, diethyl diethylpropanedioate, or diethyl 1,1-cyclobutanedicarboxylate , respectively, and 2,4-Dimethoxybenzylamine using Method CC, step 1 and Method DD steps 1 and 3.

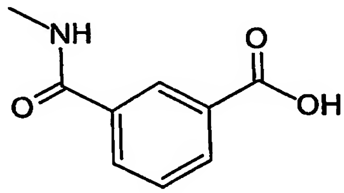
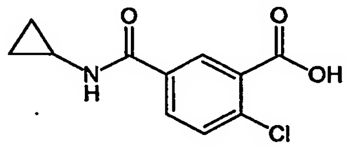
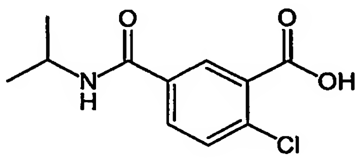
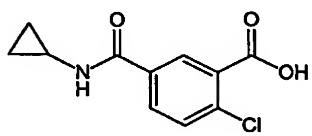
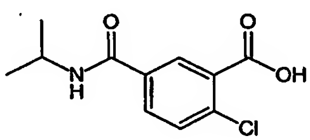
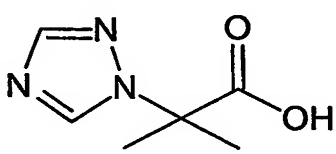
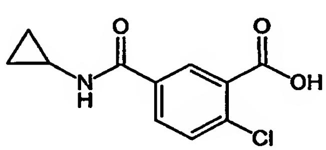
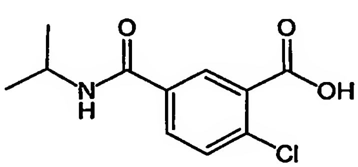
The table below lists acids 55-154, their properties, method of their synthesis as well as yields.

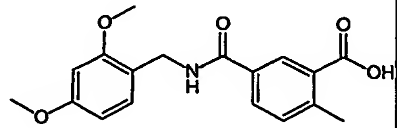
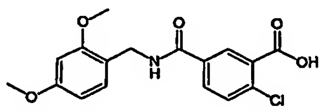
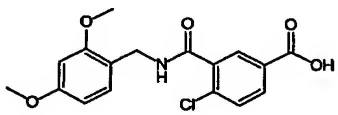
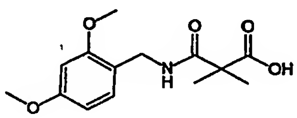
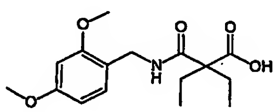
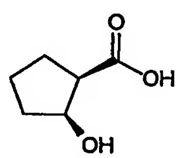
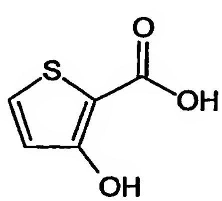
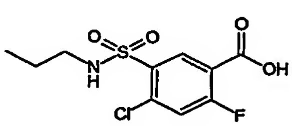
Acid #	Structure	Yield	ES-LCMS	Ion	Method
Acid 55			293.94	(M+H)	H

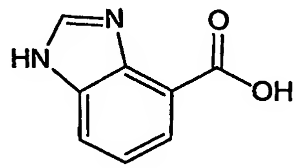
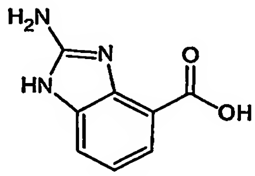
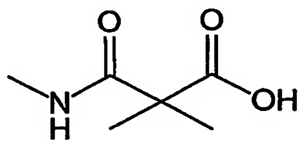
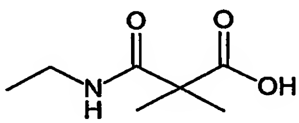
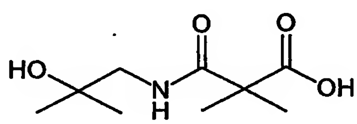
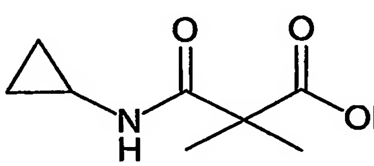
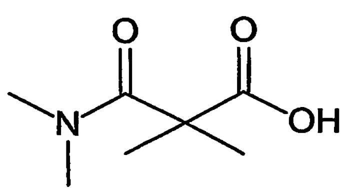
Acid 56		75	267.95	(M+H)	H
Acid 57		57	317.96	(M+Na)	H
Acid 58		85	357.92	(M+Na)	H
Acid 59		23	332	(M+Na)	H
Acid 60		77	343.97	(M+Na)	H
Acid 61		55	275.87	(M+Na)	H
Acid 62			282.08	(M+H)	H
Acid 63			310.01	(M+Na)	H

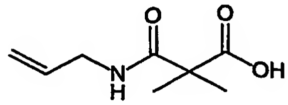
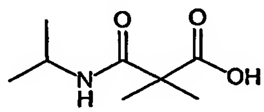
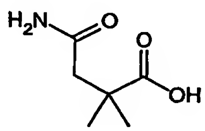
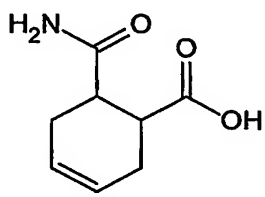
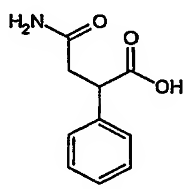
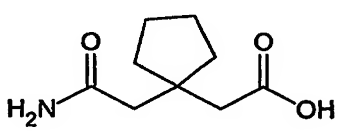
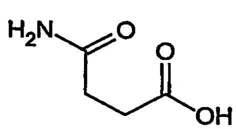
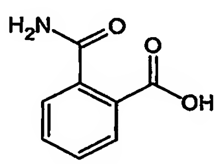
Acid 64			298.1	(M+Na)	H
Acid 65					BB
Acid 66					BB
Acid 67					BB
Acid 68					BB
Acid 69					AA
Acid 70					AA
Acid 71					AA

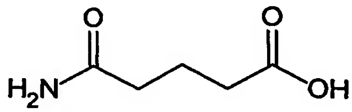
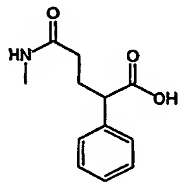
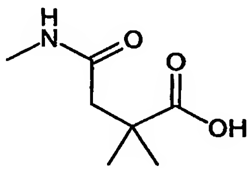
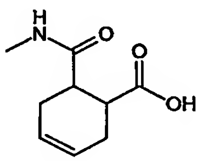
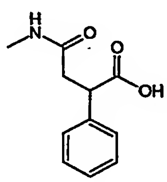
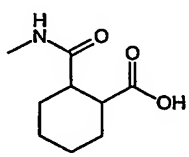
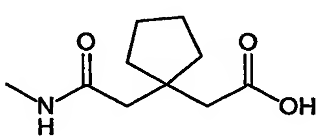
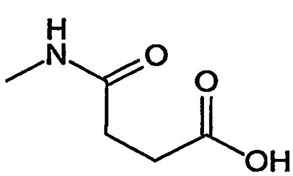
Acid 72					AA
Acid 73					AA
Acid 74					AA
Acid 75					AA
Acid 76					AA
Acid 77					AA
Acid 78					AA
Acid 79					AA

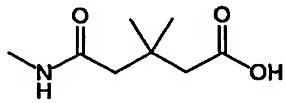
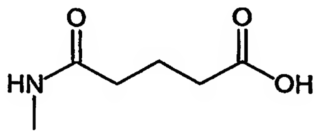
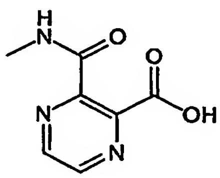
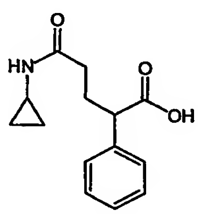
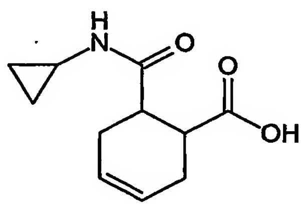
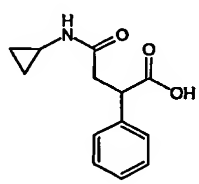
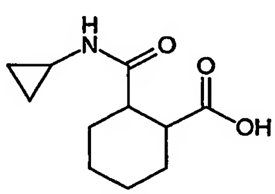
glax					
Acid 80		68	239.9	(M+H)	DD
Acid 81		73	241.91	(M+H)	DD
Acid 80		68	239.9	(M+H)	DD
Acid 81		73	241.91	(M+H)	DD
commercial					
Acid 80		68	239.9	(M+H)	DD
Acid 81		73	241.91	(M+H)	DD

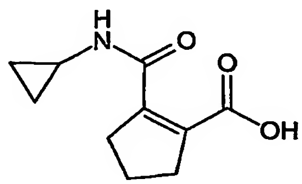
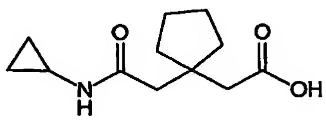
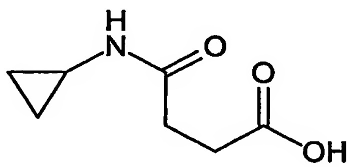
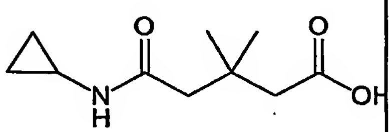
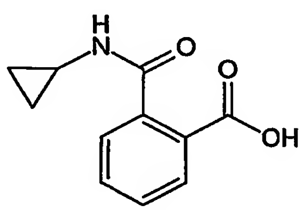
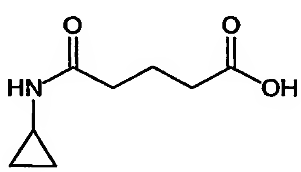
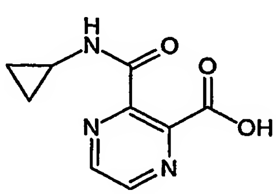
Acid 82		54	329.95	(M+H)	DD
Acid 83		94	349.89, 351.91	(M+H)	DD
Acid 84		92	349.88, 351.91	(M+H)	DD
Acid 85		100	304	(M+Na)	DD
Acid 86		82	331.98	(M+Na)	DD
commercial					
glax					
Acid 87		75	318.03	(M+Na)	H

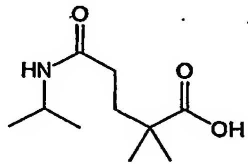
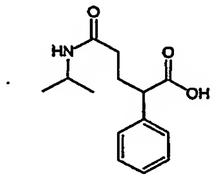
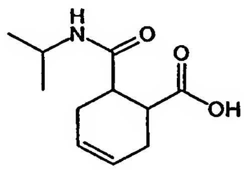
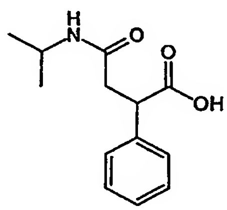
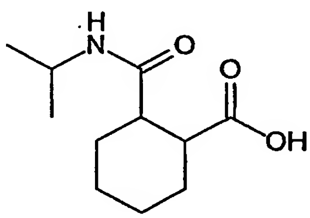
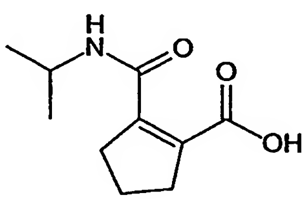
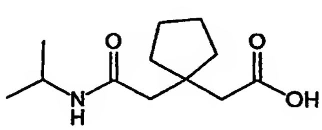
Acid 88					BB
Acid 89					BB
Acid 90					CC
Acid 91					CC
Acid 92					CC
Acid 93					CC
Acid 94					CC

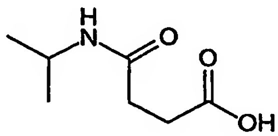
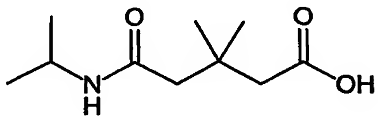
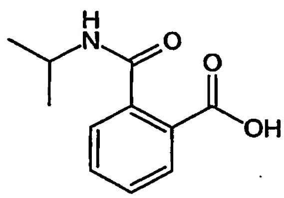
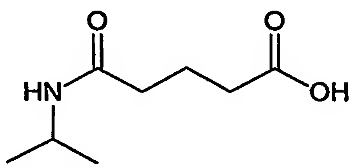
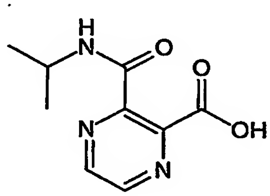
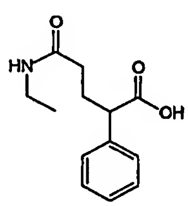
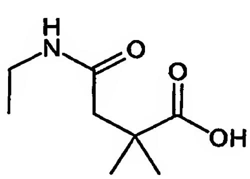
Acid 95					CC
Acid 96					CC
Acid 97					AA
Acid 98					AA
Acid 99					AA
Acid 100					AA
Acid 101					AA
Acid 102					AA

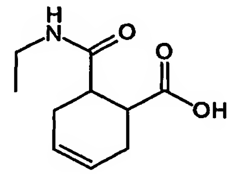
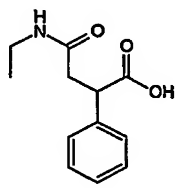
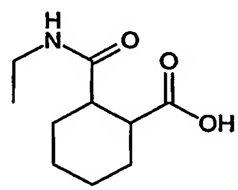
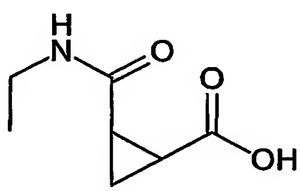
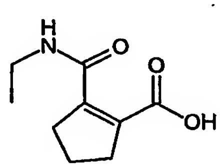
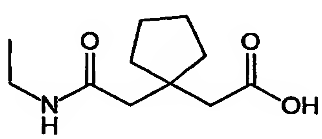
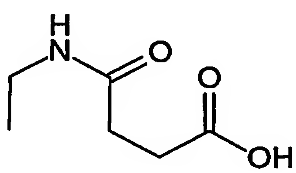
Acid 103					AA
Acid 104					AA
Acid 105					AA
Acid 106					AA
Acid 107					AA
Acid 108					AA
Acid 109					AA
Acid 110					AA

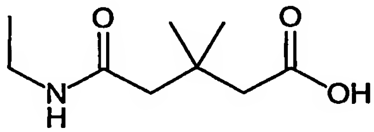
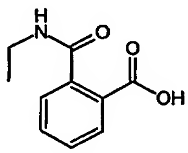
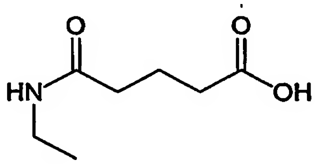
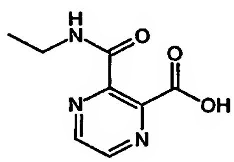
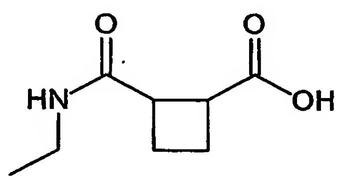
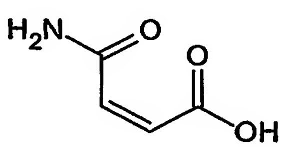
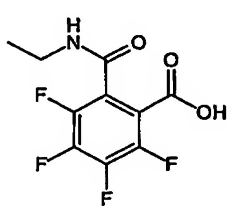
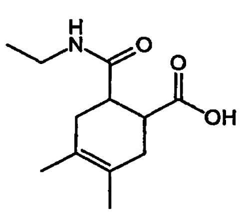
Acid 111					AA
Acid 112					AA
Acid 113					AA
Acid 114					AA
Acid 115					AA
Acid 116					AA
Acid 117					AA

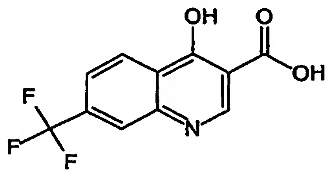
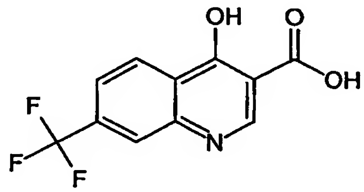
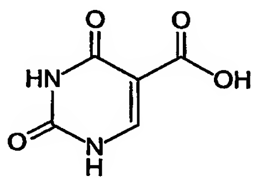
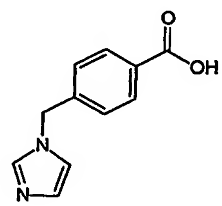
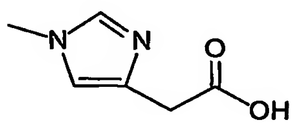
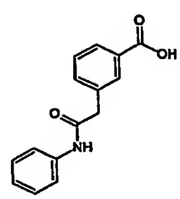
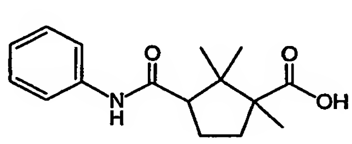
Acid 118					AA
Acid 119					AA
Acid 120					AA
Acid 121					AA
Acid 122					AA
Acid 123					AA
Acid 124					AA

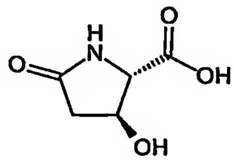
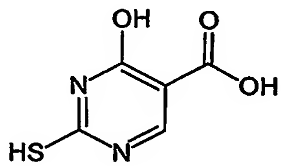
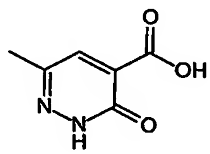
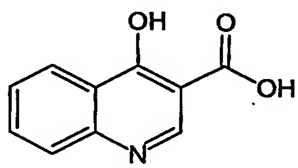
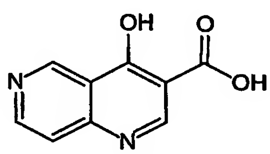
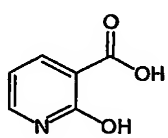
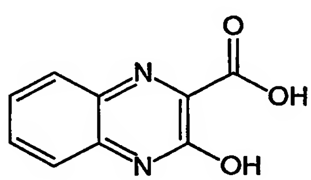
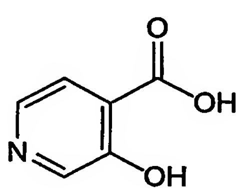
Acid 125					AA
Acid 126					AA
Acid 127					AA
Acid 128					AA
Acid 129					AA
Acid 130					AA
Acid 131					AA

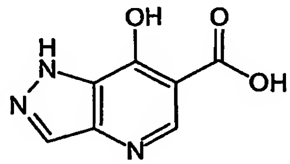
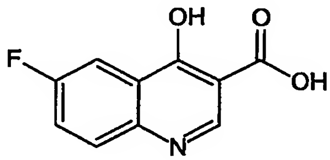
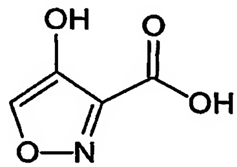
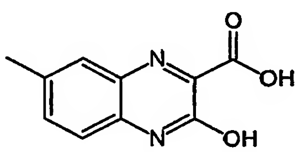
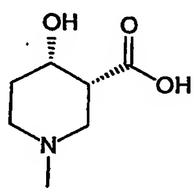
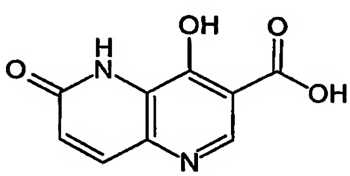
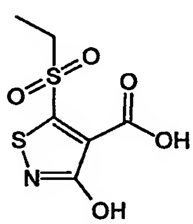
Acid 132					AA
Acid 133					AA
Acid 134					AA
Acid 135					AA
Acid 136					AA
Acid 137					AA
Acid 138					AA

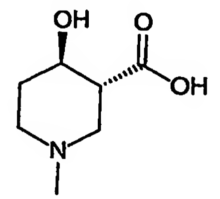
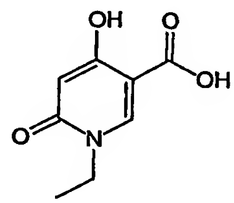
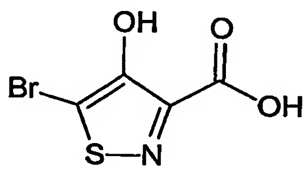
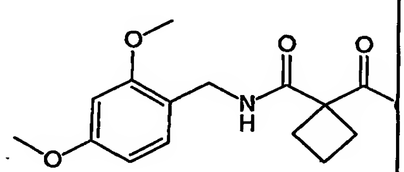
Acid 139					AA
Acid 140					AA
Acid 141					AA
Acid 142					AA
Acid 143					AA
Acid 144					AA
Acid 145					AA

Acid 146					AA
Acid 147					AA
Acid 148					AA
Acid 149					AA
Acid 150					AA
Acid 151					AA
Acid 152					AA
Acid 153					AA

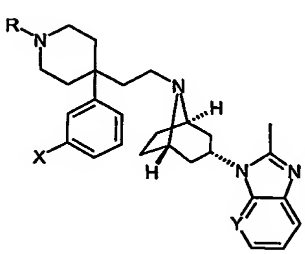
glax					
glax					
glax					
glax					
glax					
glax					
glax					

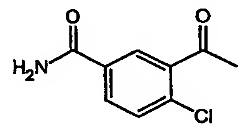
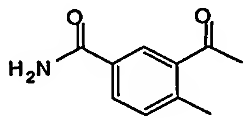
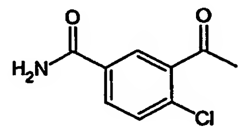
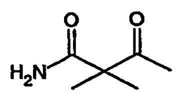
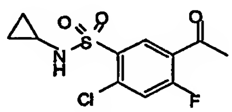
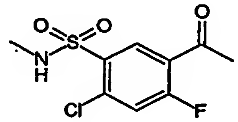
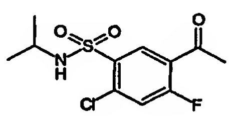
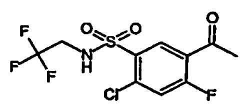
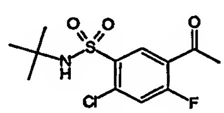
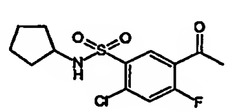
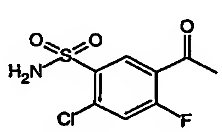
glax					
glax					
glax					
glax					
glax					
glax					
glax					
glax					

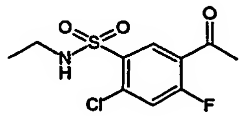
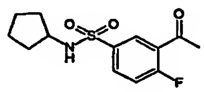
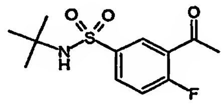
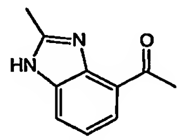
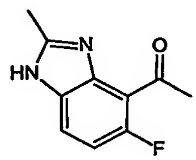
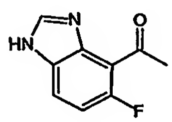
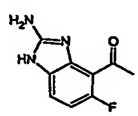
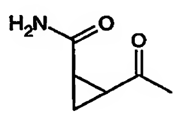
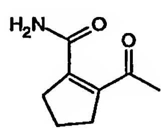
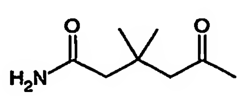
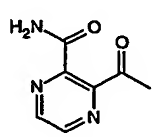
glax					
glax					
glax					
glax					
glax					
glax					
glax					

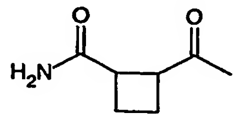
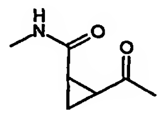
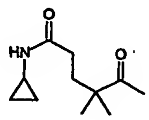
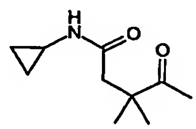
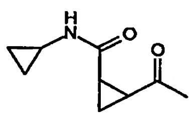
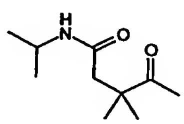
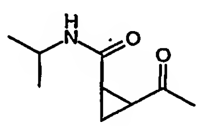
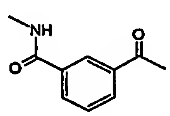
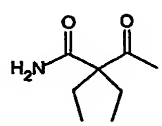
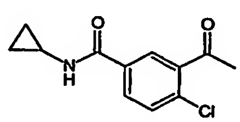
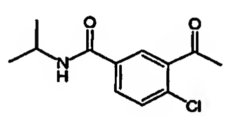
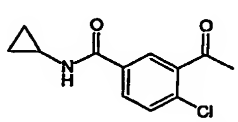
glax glax glax	  				
Acid 154		83	315.94	(M+Na)	DD

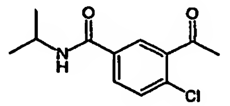
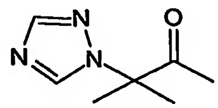
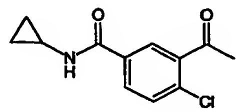
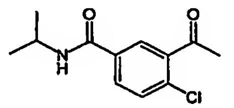
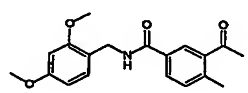
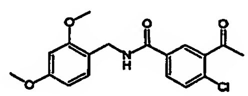
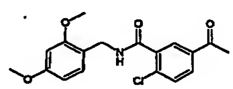
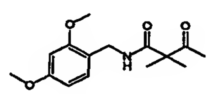
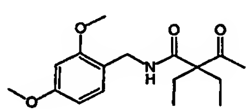
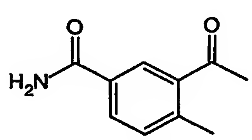
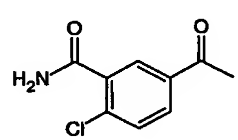
The following examples were prepared using acids described elsewhere in this invention

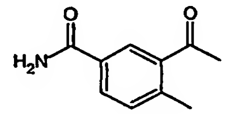
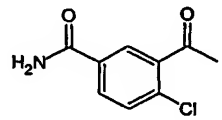
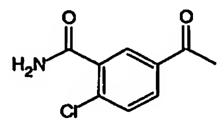
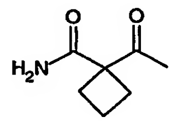
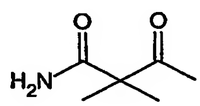
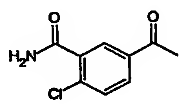
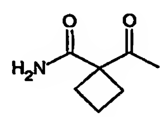
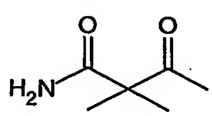
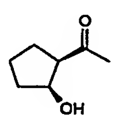
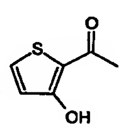
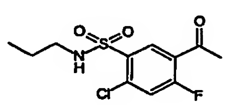


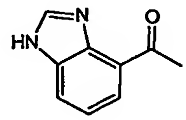
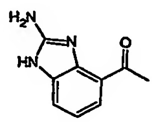
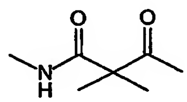
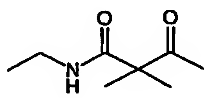
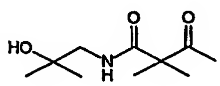
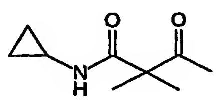
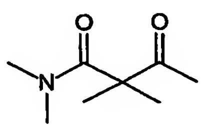
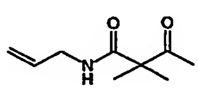
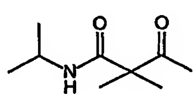
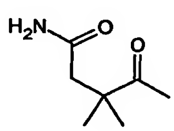
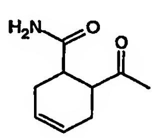
Example	Acid # or source	R	X	Y	% Yield	LCMS ES	Ion	Method
1021	Acid 83		H	C	36	610.18	(M+H)	F
1022	Acid 82		CH3	C	52	604.24	(M+H)	F
1023	Acid 83		CH3	C	52	624.22	(M+H)	F
1024	Acid 85		CH3	C	38	556.27	(M+H)	F
1025	Acid 55		F	C	42	722.36	(M+H)	A
1026	Acid 56		F	C	36	696.18	(M+H)	A
1027	Acid 57		F	C	52	724.38	(M+H)	A
1028	Acid 58		F	C	56	764.33	(M+H)	A
1029	Acid 59		F	C	32	738.37	(M+H)	A
1030	Acid 60		F	C	50	750.23	(M+H)	A
1031	Acid 61		F	C	49	682.32	(M+H)	A

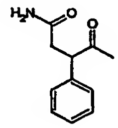
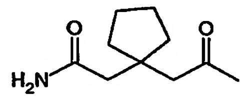
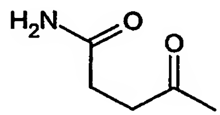
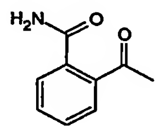
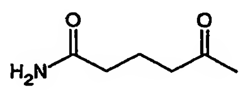
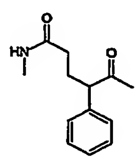
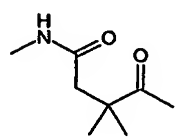
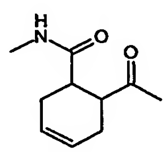
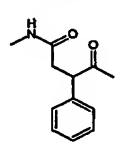
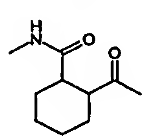
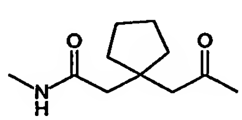
1032	Acid 62		F	C	54	710.34	(M+H)	A
1033	Acid 63		F	C	26	716.42	(M+H)	A
1034	Acid 64		F	C	29	704.42	(M+H)	A
1035	Acid 65		F	C	28	605.35	(M+H)	A
1036	Acid 66		F	C	48	623.32	(M+H)	A
1037	Acid 67		F	C	46	609.28	(M+H)	A
1038	Acid 68		F	C	13	624.34	(M+H)	A
1039	Acid 69		F	C	44	558.38	(M+H)	A
1040	Acid 70		F	C	57	584.39	(M+H)	A
1041	Acid 71		F	C	58	588.45	(M+H)	A
1042	Acid 72		F	C	52	596.35	(M+H)	A

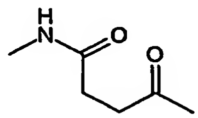
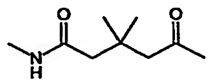
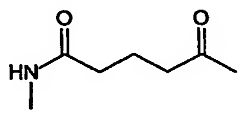
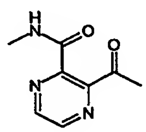
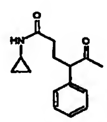
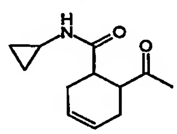
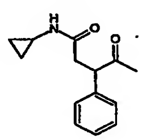
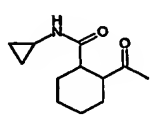
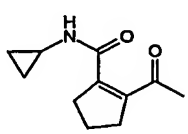
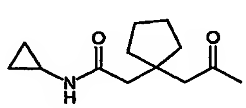
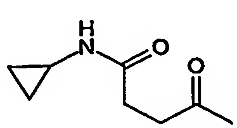
1043	Acid 73		F	C	23	572.34	(M+H)	A
1044	Acid 74		F	C	41	572.35	(M+H)	A
1045	Acid 75		F	C	29	628.39	(M+H)	A
1046	Acid 76		F	C	43	614.42	(M+H)	A
1047	Acid 77		F	C	64	598.42	(M+H)	A
1048	Acid 78		F	C	27	616.5	(M+H)	A
1049	Acid 79		F	C	39	600.45	(M+H)	A
1050	glax		F	C	37	608.4	(M+H)	A
1051	Acid 86		F	C	37	588.4	(M+H)	A
1052	Acid 80		H	C	48	650.19	(M+H)	A
1053	Acid 81		H	C	39	652.22	(M+H)	A
1054	Acid 80		F	C	56	668.22	(M+H)	A

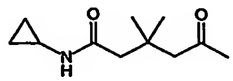
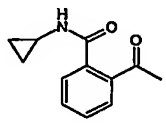
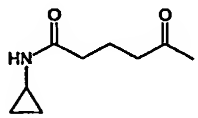
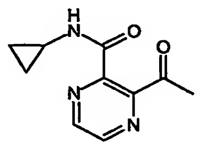
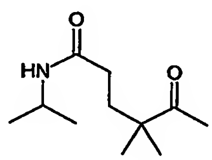
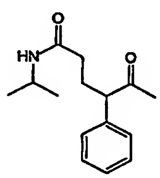
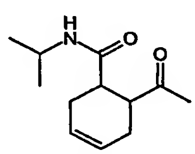
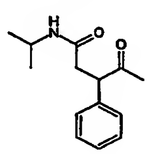
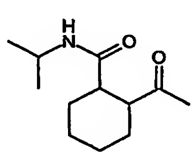
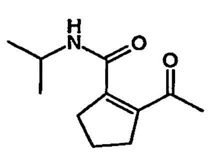
1055	Acid 81		F	C	43	670.21	(M+H)	A
1056	commercial		F	C	39	584.24	(M+H)	A
1057	Acid 80		CH3	C	41	664.25	(M+H)	A
1058	Acid 81		CH3	C	41	666.26	(M+H)	A
1059	Acid 82		F	C	45	758.33	(M+H)	A
1060	Acid 83		F	C	36	778.29	(M+H)	A
1061	Acid 84		F	C	66	778.29	(M+H)	A
1062	Acid 85		F	C	41	710.28	(M+H)	A
1063	Acid 86		F	C	56	738.33	(M+H)	A
1064	Acid 82		H	C	39	590.25	(M+H)	F
1065	Acid 84		H	C	13	610.18	(M+H)	F

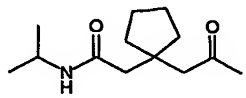
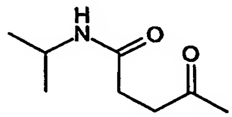
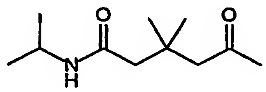
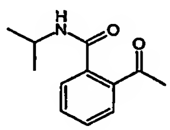
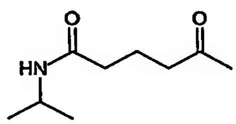
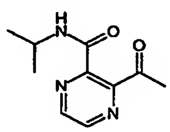
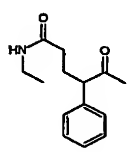
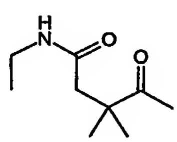
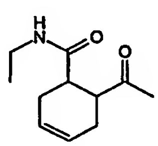
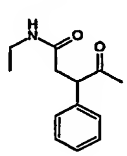
1066	Acid 82		F	C	48	608.24	(M+H)	F
1067	Acid 83		F	C	53	628.18	(M+H)	F
1068	Acid 84		F	C	47	628.17	(M+H)	F
1069	Acid 154		F	C	46	572.27	(M+H)	F
1070	Acid 85		F	C	33	560.26	(M+H)	F
1071	Acid 84		CH 3	C	23	624.24	(M+H)	F
1072	Acid 154		CH 3	C	34	568.28	(M+H)	F
1073	Acid 85		H	C	18	542.29	(M+H)	F
1075	comm ercial		F	C	49	559.14	(M+H)	A
1076	glax		F	C	39	573.05	(M+H)	A
1077	Acid 87		F	C	52	724.38	(M+H)	A

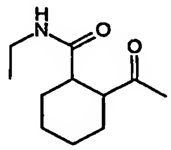
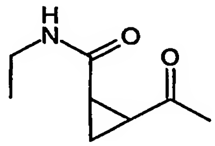
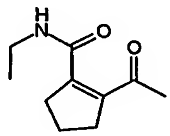
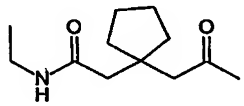
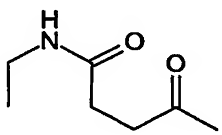
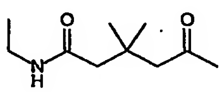
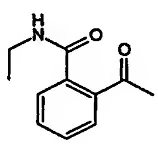
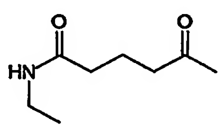
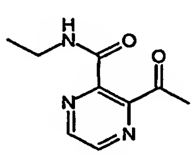
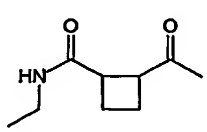
1078	Acid 88		F	C	27	591.27	(M+H)	A
1079	Acid 89		F	C	22	606.35	(M+H)	A
1080	Acid 90		F	C	24	574.35	(M+H)	A
1081	Acid 91		F	C	34	588.36	(M+H)	A
1082	Acid 92		F	C	23	632.47	(M+H)	A
1083	Acid 93		F	C	33	598.79	(M-1)	A
1084	Acid 94		F	C	18	588.33	(M+H)	A
1085	Acid 95		F	C	41	600.37	(M+H)	A
1086	Acid 96		F	C	45	602.4	(M+H)	A
1087	Acid 97		F	C	33	574.36	(M+H)	A
1088	Acid 98		F	C	32	598.39	(M+H)	A

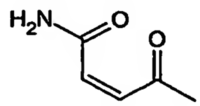
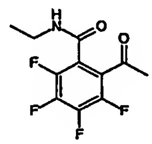
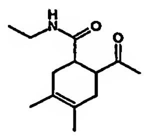
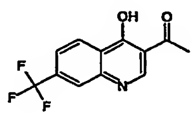
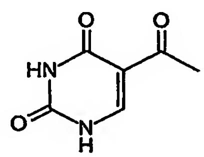
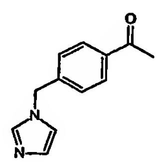
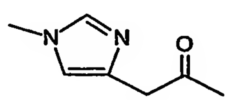
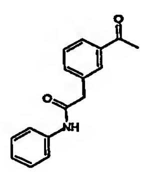
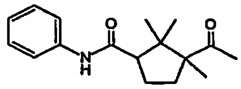
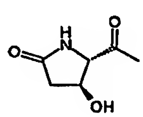
1089	Acid 99		F	C	49	622.42	(M+H)	A
1090	Acid 100		F	C	55	614.44	(M+H)	A
1091	Acid 101		F	C	50	546.36	(M+H)	A
1092	Acid 102		F	C	15	594.37	(M+H)	A
1093	Acid 103		F	C	54	560.41	(M+H)	A
1094	Acid 104		F	C	27	650.43	(M+H)	A
1095	Acid 105		F	C	40	610.32	(M+H)	A
1096	Acid 106		F	C	42	612.35	(M+H)	A
1097	Acid 107		F	C	27	636.39	(M+H)	A
1098	Acid 108		F	C	31	614.39	(M+H)	A
1099	Acid 109		F	C	31	628.44	(M+H)	A

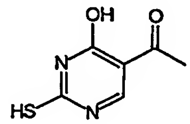
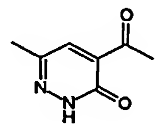
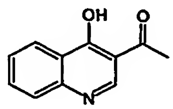
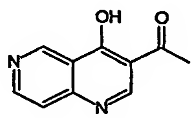
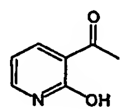
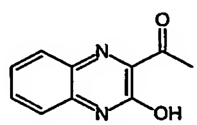
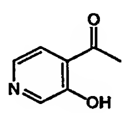
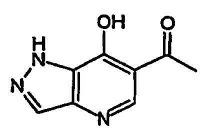
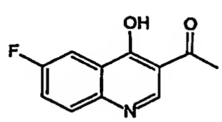
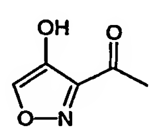
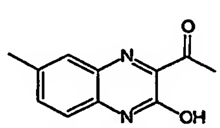
1100	Acid 110		F	C	34	560.37	(M+H)	A
1101	Acid 111		F	C	40	602.38	(M+H)	A
1102	Acid 112		F	C	39	574.4	(M+H)	A
1103	Acid 113		F	C	34	610.35	(M+H)	A
1104	Acid 114		F	C	20	676.4	(M+H)	A
1105	Acid 115		F	C	31	638.38	(M+H)	A
1106	Acid 116		F	C	27	662.42	(M+H)	A
1107	Acid 117		F	C	25	640.49	(M+H)	A
1108	Acid 118		F	C	37	624.44	(M+H)	A
1109	Acid 119		F	C	19	654.44	(M+H)	A
1110	Acid 120		F	C	53	586.41	(M+H)	A

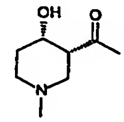
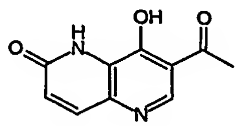
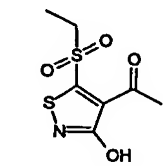
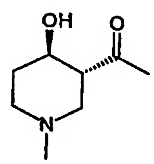
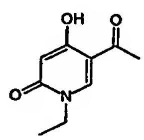
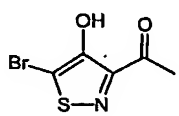
1111	Acid 121		F	C	29	628.44	(M+H)	A
1112	Acid 122		F	C	41	634.42	(M+H)	A
1113	Acid 123		F	C	47	600.45	(M+H)	A
1114	Acid 124		F	C	31	636.36	(M+H)	A
1115	Acid 125		F	C	21	630.43	(M+H)	A
1116	Acid 126		F	C	24	678.51	(M+H)	A
1117	Acid 127		F	C	38	640.51	(M+H)	A
1118	Acid 128		F	C	33	664.5	(M+H)	A
1119	Acid 129		F	C	35	642.51	(M+H)	A
1120	Acid 130		F	C	38	626.47	(M+H)	A

1121	Acid 131		F	C	15	656.49	(M+H)	A
1122	Acid 132		F	C	34	588.45	(M+H)	A
1123	Acid 133		F	C	36	630.51	(M+H)	A
1124	Acid 134		F	C	33	636.45	(M+H)	A
1125	Acid 135		F	C	34	602.48	(M+H)	A
1126	Acid 136		F	C	29	638.43	(M+H)	A
1127	Acid 137		F	C	20	664.52	(M+H)	A
1128	Acid 138		F	C	25	602.45	(M+H)	A
1129	Acid 139		F	C	26	626.45	(M+H)	A
1130	Acid 140		F	C	31	650.51	(M+H)	A

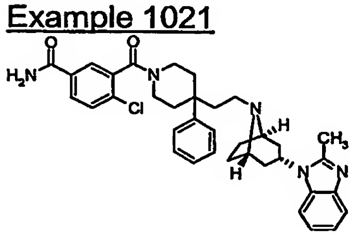
1131	Acid 141		F	C	25	628.52	(M+H)	A
1132	Acid 142		F	C	44	586.42	(M+H)	A
1133	Acid 143		F	C	34	612.49	(M+H)	A
1134	Acid 144		F	C	18	640.49	(M+H)	A
1135	Acid 145		F	C	41	574.43	(M+H)	A
1136	Acid 146		F	C	23	616.48	(M+H)	A
1137	Acid 147		F	C	25	622.44	(M+H)	A
1138	Acid 148		F	C	37	588.45	(M+H)	A
1139	Acid 149		F	C	35	624.44	(M+H)	A
1140	Acid 150		F	C	35	600.46	(M+H)	A

1141	Acid 151		F	C	33	544.35	(M+H)	A
1142	Acid 152		F	C	15	694.34	(M+H)	A
1143	Acid 153		F	C	14	654.43	(M+H)	A
1144	glax		F	C	52	686.4	(M+H)	A
1145	glax		F	C	18	585.34	(M+H)	A
1146	glax		F	C	29	631.37	(M+H)	A
1147	glax		F	C	30	569.35	(M+H)	A
1148	glax		F	C	30	684.4	(M+H)	A
1149	glax		F	C	12	704.44	(M+H)	A
1150	glax		F	C	11	574.41	(M+H)	A

1151	glax		F	C	45	601.36	(M+H)	A
1152	glax		F	C	65	583.38	(M+H)	A
1153	glax		F	C	47	618.41	(M+H)	A
1154	glax		F	C	17	619.39	(M+H)	A
1155	glax		F	C	54	568.38	(M+H)	A
1156	glax		F	C	63	619.4	(M+H)	A
1157	glax		F	C	44	568.37	(M+H)	A
1158	glax		F	C	15	608.43	(M+H)	A
1159	glax		F	C	38	636.4	(M+H)	A
1160	glax		F	C	13	558.36	(M+H)	A
1161	glax		F	C	76	633.43	(M+H)	A

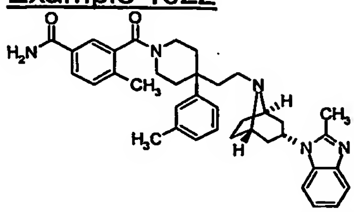
1162	glax		F	C	47	588.45	(M+H)	A
1163	glax		F	C	12	635.45	(M+H)	A
1164	glax		F	C	23	666.36	(M+H)	A
1165	glax		F	C	70	588.45	(M+H)	A
1166	glax		F	C	41	612.41	(M+H)	A
1167	glax		F	C	20	652.26	(M+H)	A

Example 1021



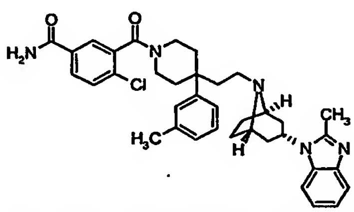
4-chloro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzamide. ^{1}H NMR (300 MHz, CD_3OD) δ 7.96-7.07(m, 12H), 4.75(m, 1H), 4.21 (m, 1H), 3.90-3.10(m, 6H), 2.53 (s, 3H), 2.50-1.68 (m, 15H).

Example 1022



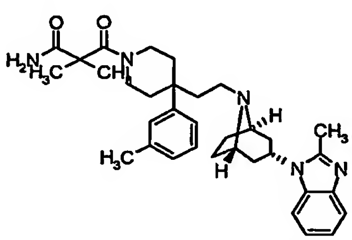
4-methyl-3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)-1-piperidinyl]carbonyl}benzamide. . ^{1}H NMR (300 MHz, CD_3OD) δ 7.96-7.07(m, 11H), 4.75(m, 1H), 4.31-4.15(m, 1H), 3.91-3.10(m, 6H), 2.53 (s, 3H), 2.50-1.68 (m, 15H), 2.43(s, 1.5H), 2.38 (s, 3H), 2.25(s, 1.5H).

Example 1023



4-chloro-3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)-1-piperidinyl]carbonyl}benzamide. ^{1}H NMR (300 MHz, CD_3OD) δ 7.96-7.07(m, 11H), 4.75(m, 1H), 4.22 (m, 1H), 3.80-3.16(m, 6H), 2.53 (s, 3H), 2.50-1.68 (m, 15H), 2.38 (s, 3H).

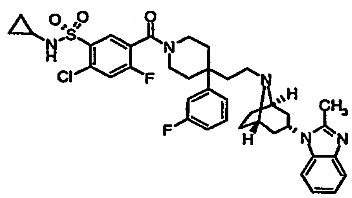
Example 1024



2,2-dimethyl-3-[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)-1-piperidinyl]-3-

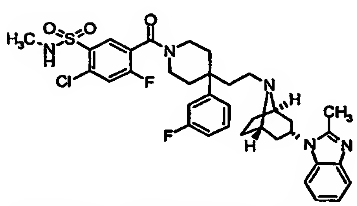
oxopropanamide. ^{1}H NMR (300 MHz, CD_3OD) δ 7.55-7.06(m, 8H), 4.77(m, 1H), 4.02 (m, 1H), 3.89-3.17(m, 6H), 2.67-1.68 (m, 21H), 2.56 (s, 3H), 2.37 (s, 3H).

Example 1025



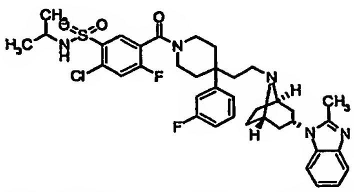
2-chloro-N-cyclopropyl-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.18(m, 1H), 7.67(d, J=8.8Hz, 1H), 7.58(m, 1H), 7.47(m, 2H), 7.30(s, 1H), 7.29-7.20(m, 3H), 7.05(m, 1H), 4.79(m, 1H), 4.21(m, 1H), 3.60-3.25(m, 8H), 2.59(s, 3H), 2.52-1.70(m, 15H), 0.56(m, 4H).

Example 1026



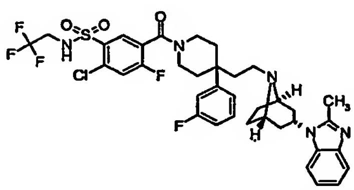
2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.09(m, 1H), 7.60(d, J=8.8Hz, 1H), 7.53(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.75(m, 1H), 4.16(m, 1H), 3.53-3.18(m, 8H), 2.55(d, J=9.3Hz, 3H), 2.52-1.70(m, 16H).

Example 1027



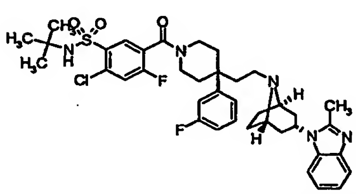
2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-(1-methylethyl)benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.11(m, 1H), 7.60(d, *J*=8.8Hz, 1H), 7.53(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.17(m, 1H), 3.53-3.18(m, 8H), 2.53(s, 3H), 2.52-1.70(m, 14H), 1.07 (d, *J*=6.5Hz, 6H).

Example 1028



2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-(2,2,2-trifluoroethyl)benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.10(m, 1H), 7.60(d, *J*=8.8Hz, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.16(m, 1H), 3.77 (q, *J*=9.4 Hz, 2 H), 3.53-3.18(m, 8H), 2.53(s, 3H), 2.52-1.68(m, 13H).

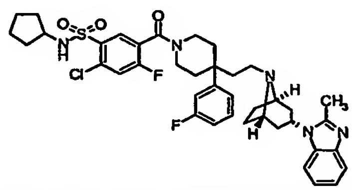
Example 1029



2-chloro-N-(1,1-dimethylethyl)-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-

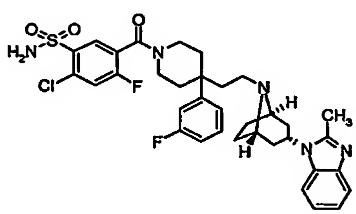
piperidinyl)carbonyl]benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.10(m, 1H), 7.58(d, J=8.8Hz, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.17(m, 1H), 3.53-3.18(m, 8H), 2.53(s, 3H), 2.52-1.69(m, 13H), 1.20(s, 9H).

Example 1030



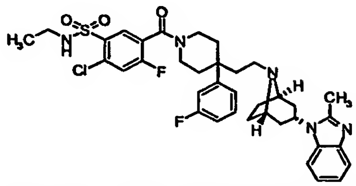
2-chloro-N-cyclopentyl-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.11(m, 1H), 7.60(d, J=8.8Hz, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.72(m, 1H), 4.16(m, 1H), 3.57-3.18(m, 8H), 2.53(s, 3H), 2.52-1.39(m, 22H).

Example 1031



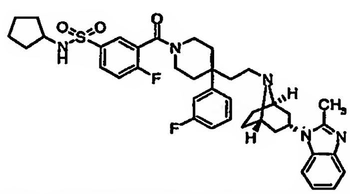
2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.10(m, 1H), 7.58(d, J=9.0Hz, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.16(m, 1H), 3.52-3.19(m, 8H), 2.53(s, 3H), 2.52-1.69(m, 13H).

Example 1032



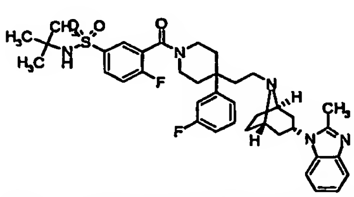
2-chloro-N-ethyl-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 8.09(m, 1H), 7.59(d, *J*=9.1Hz, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.16(m, 1H), 3.52-3.19(m, 8H), 2.97(q, *J*=7.2Hz, 2H), 2.53(s, 3H), 2.52-1.69(m, 13H), 1.06(t, *J*=7.2Hz, 3H).

Example 1033



N-cyclopentyl-4-fluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 7.98(m, 1H), 7.88(m, 1H), 7.53(m, 1H), 7.41(m, 3H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.17(m, 1H), 3.60-3.18(m, 8H), 2.52(s, 3H), 2.52-1.34(m, 22H).

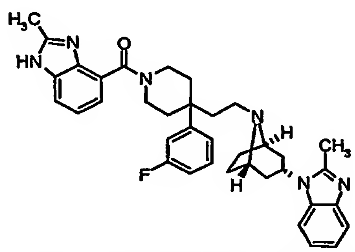
Example 1034



N-(1,1-dimethylethyl)-4-fluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-

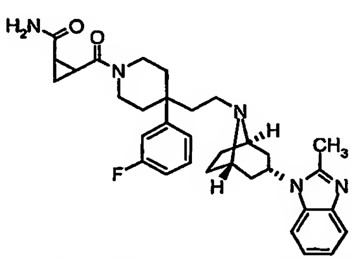
piperidinyl)carbonyl]benzenesulfonamide. [1]H NMR (300 MHz, CD_3OD) □ ppm 8.01(m, 1H), 7.89(m, 1H), 7.52(m, 1H), 7.40(m, 3H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.17(m, 1H), 3.52-3.17(m, 8H), 2.53(s, 3H), 2.52-1.68(m, 13H), 1.19(s, 9H).

Example 1035



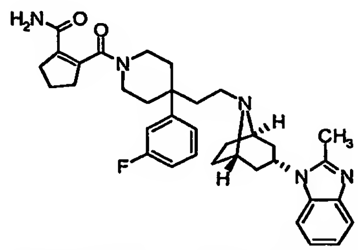
1-[(1R,5S)-8-(2-{4-(3-fluorophenyl)-1-[(2-methyl-1H-benzimidazol-4-yl)carbonyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole. [1]H NMR (300 MHz, CD_3OD) □ ppm 8.01-6.94(m, 11H), 4.90-4.72(m, 1H), 3.97(m, 1H), 3.70-3.16(m, 8H), 2.65(s, 3H), 2.55(s, 3H), 2.46-1.38(m, 14H).

Example 1039



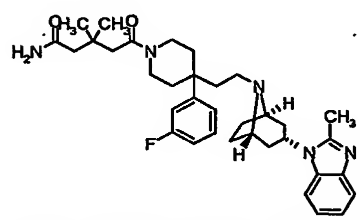
2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopropanecarboxamide. [1]H NMR (300 MHz, CD_3OD) □ ppm 7.53(m, 1H), 7.40(m, 2H), 7.25-7.14(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 4.11-3.79(m, 2H), 3.52-3.29(m, 7H), 3.08(m, 1H), 2.55(s, 3H), 2.52-1.17(m, 16H).

Example 1040



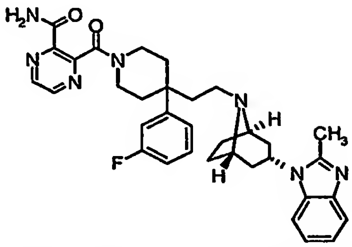
2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-cyclopentene-1-carboxamide. [1]H NMR (300 MHz, CD_3OD) □ ppm 7.53(m, 1H), 7.41(m, 2H), 7.25-7.14(m, 4H), 6.97(m, 1H), 4.74(m, 1H), 4.0(m, 1H), 3.55(m, 1H), 3.35-3.20(m, 5H), 3.00(m, 1H), 2.54(s, 3H), 2.80-1.17(m, 20H).

Example 1041



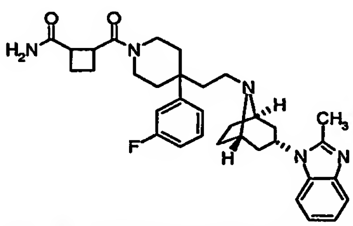
5-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-5-oxopentanamide. [1]H NMR (300 MHz, CD_3OD) □ ppm 7.50(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 4.00(m, 1H), 3.83(m, 1H), 3.42-1.68(m, 24H), 2.55(s, 3H), 1.10(d, J=3.8Hz, 6H).

Example 1042



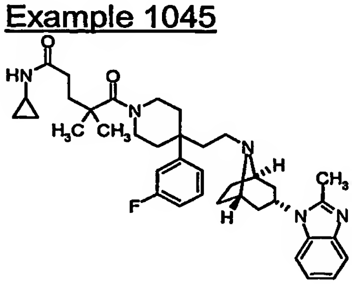
3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-pyrazinecarboxamide. [1]H NMR (300 MHz, CD_3OD) □ ppm 8.78(d, *J*=2.5Hz, 1H), 8.73(d, *J*=2.5Hz, 1H), 7.52(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 4.15(m, 1H), 3.46-1.68(m, 21H), 2.52(s, 3H).

Example 1043



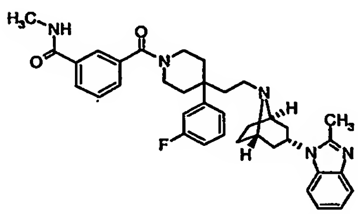
2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclobutanecarboxamide. [1]H NMR (300 MHz, CD_3OD) □ ppm 7.52(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 6.97(m, 1H), 4.73(m, 1H), 4.15-1.68(m, 28H), 2.55(s, 3H).

Example 1045



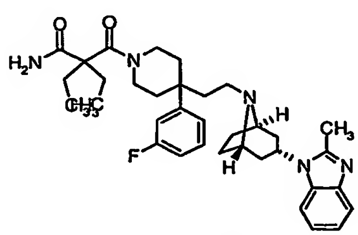
N-cyclopropyl-5-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-4,4-dimethyl-5-oxopentanamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 7.52(m, 1H), 7.40(m, 2H), 7.25-7.12(m, 4H), 6.96(m, 1H), 4.75(m, 1H), 3.98(m, 1H), 3.36-1.68(m, 28H), 2.55(s, 3H).

Example 1050



3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzamide. ^{1}H NMR (300 MHz, CD_3OD) □ ppm 7.85(m, 1H), 7.84(m, 1H), 7.55(m, 3H), 7.40(m, 2H), 7.26-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.13(m, 1H), 3.58(m, 1H), 3.46-1.68(m, 20H), 2.91(s, 3H), 2.51(s, 3H).

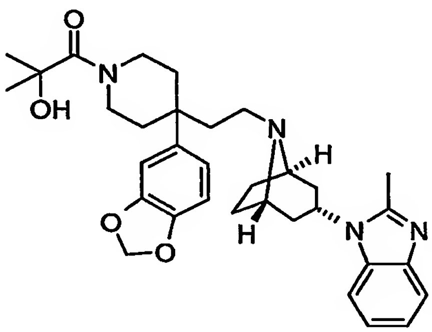
Example1051



2-ethyl-2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]butanamide. ^{1}H NMR (300 MHz, CD_3OD) δ 7.52(m, 1H), 7.41(m, 2H), 7.26-7.16(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 3.97 (m, 1H), 3.67 (m, 1H), 3.34-3.21(m, 5H), 2.55(s, 3H), 2.41(m, 2H), 2.22(m, 2H), 2.03-1.69(m, 15H),0.80(m, 6H).

Example 1168

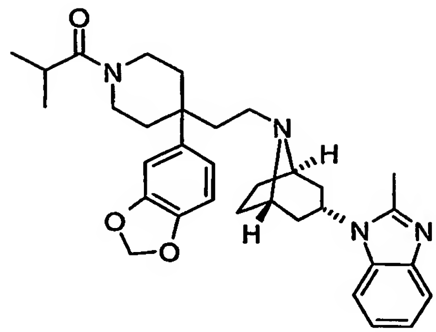
Preparation of
1-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2-methyl-1-oxopropan-2-ol



A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.17 mL, 1.25 mmol) and 2-hydroxyisobutyric acid (41 mg, 0.39 mmol) in dimethylformamide (1.25 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (163 mg, 0.43 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution, with water, dried and purified by chromatography on silica gel eluting with a dichloromethane to methanol-dichloromethane 1:19 gradient to give 1-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2-methyl-1-oxopropan-2-ol as a solid (0.10g, 44%). HRMS $C_{33}H_{42}N_4O_4$ *m/z* 559.3284 $(M+H)_{Cal.}$ 559.3276 $(M+H)_{Obs.}$.

Example 1169

Preparation of
1-((1*R*,5*S*)-8-{2-[4-(1,3-benzodioxol-5-yl)-1-isobutyrylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

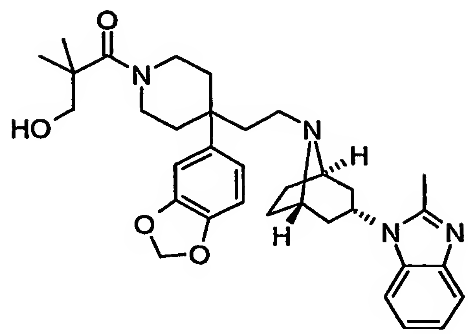


A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.17 mL, 1.25 mmol) and isobutyric acid (34 mg, 0.39 mmol) in dimethylformamide (1.25 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (163 mg, 0.43 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution, with water and dried to give 1-((1*R*,5*S*)-8-{2-[4-(1,3-benzodioxol-5-yl)-1-isobutyrylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole as a solid (0.15g, 72%). HRMS $C_{33}H_{42}N_4O_3$ *m/z* 543.3335 $(M+H)_{Cal.}$ 543.3322 $(M+H)_{Obs.}$.

Example 1170

Preparation of

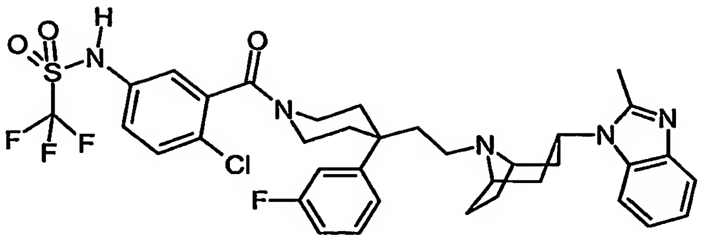
3-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol

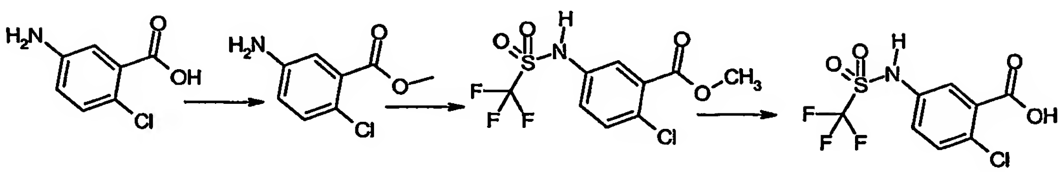


A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.17 mL, 1.25 mmol) and 2,2-dimethyl-3-hydroxypropionic acid (46 mg, 0.39 mmol) in dimethylformamide (1.25 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (163 mg, 0.43 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting gummy precipitate was dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, with water, dried and purified by chromatography on silica gel eluting with a dichloromethane to methanol-dichloromethane 1:9 gradient to give 3-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol as a solid (0.13g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.29 (m, 1H), 7.15 (m, 2H), 6.80 (m, 2H), 6.73 (m, 1H), 5.97 (s, 2H), 4.62 (m, 1H), 3.92 (m, 2H), 3.75 (m, 1H), 3.46 (s, 2H), 3.26 (m, 4H), 2.57 (s, 3H), 2.38 (m, 2H), 2.14 (m, 2H), 1.91 – 2.00 (m, 6H), 1.70 – 1.78 (m, 4H), 1.64 (m, 2H), 1.25 (s, 6H). HRMS $C_{34}H_{44}N_4O_4$ *m/z* 573.3441 $(M+H)_{Cal.}$ 573.3428 $(M+H)_{Obs.}$.

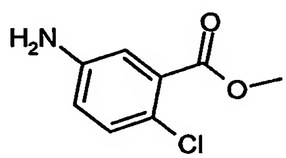
Example 1171

N-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide.



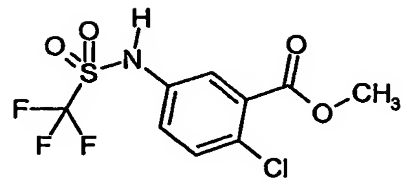


a) Preparation of methyl 5-amino-2-chlorobenzoate.



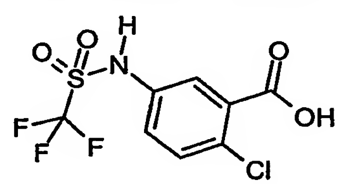
To a solution of 5-amino-2-chlorobenzoic acid (6.0 g, 35 mmol) in anhydrous methanol (100 ml) was added dropwise thionyl chloride (15 ml) with stirring under a nitrogen atmosphere. After stirring for 3 hours the volatiles were removed by spin evaporation in vacuo and the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate and then water. The organic layer was concentrated by spin evaporation in vacuo with the addition of dichloromethane (3 times) to give methyl 5-amino-2-chlorobenzoate as a white solid (6.2 g, 95%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.20-7.14 (m, 1H), 7.13-7.02 (m, 1H), 6.73-6.67 (m. 1H), 3.89 (s, 3H). ES-LCMS *m/z* 186 (M+H).

b) Preparation of methyl 2-chloro-5-{[(trifluoromethyl)sulfonyl]amino}benzoate.



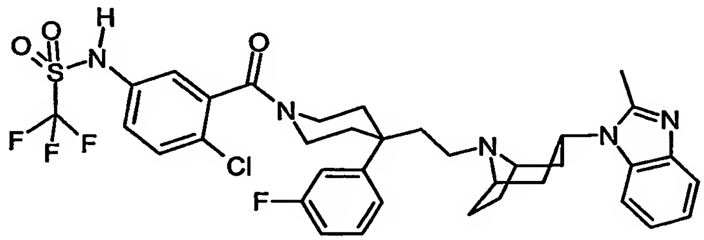
Triflic anhydride (1.53 g, 5.39 mmol) was added dropwise to a solution of methyl 5-amino-2-chlorobenzoate (2.0 g, 10.8 mmol) in dichloromethane (35 ml) at 0 °C while stirring under a nitrogen atmosphere. After warming to room temperature over 1 hour, the thick slurry was diluted with additional dichloromethane (200 ml) and washed with aqueous 1 N hydrochloric acid and then water. The dichloromethane layer was dried with $MgSO_4$ and the volatiles were removed by spin evaporation in vacuo to give methyl 2-chloro-5-{[(trifluoromethyl)sulfonyl]amino}benzoate as a tan oil (1.7 g, 100%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.43 (s, 1H), 7.55-7.18 (m, 5H), 3.92-3.82 (m, 2H), 3.31-3.18 (m, 2H), 2.40-1.92 (m, 4H), and 1.38 (s, 9H). ES-LCMS *m/z* 317 (M+H).

c) Preparation of 2-chloro-5-{[(trifluoromethyl)sulfonyl]amino}benzoic acid.



A solution of methyl 2-chloro-5-{[(trifluoromethyl)sulfonyl]amino}benzoate (1.0 g, 3.15 mmol), sodium hydroxide (378 mg, 9.44 mmol), methanol (6 ml) and water (6 ml) was stirred for 1 hour. Removal of the volatiles by spin evaporation in vacuo gave a residue that was dissolved in 1 N aqueous hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 times) and the organic layers were combined, washed with water, and concentrated by spin evaporation in vacuo to give 2-chloro-5-{[(trifluoromethyl)sulfonyl]amino}benzoic acid as a crystalline solid (0.78 g, 82%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.63-7.60 (m, 1H), 7.59-7.54 (m, 1H), 7.40-7.35 (m, 1H). ES-LCMS *m/z* 304 (M+H).

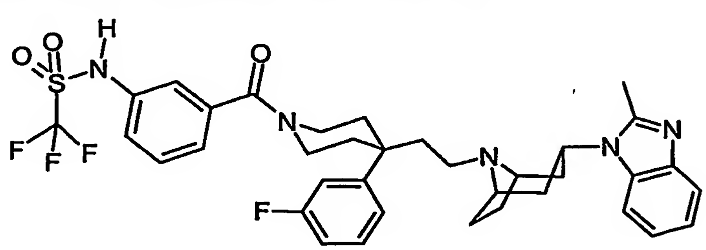
d) Preparation of N-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide.

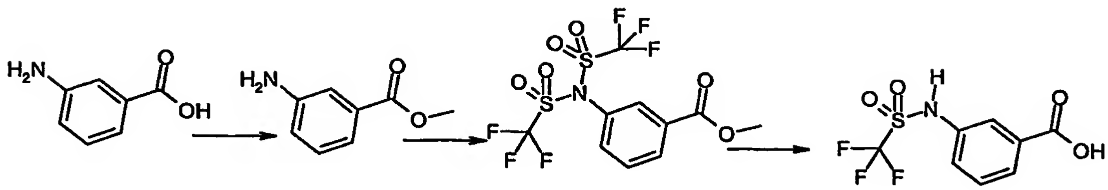


N-{4-Chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (43m g, 23 %) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-chloro-5-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (82 mg. 270 mmol), HATU (140 mg, 389 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ^{1}H-NMR (400 MHz, DMSO-d_6): 8.6 (bs, 1H), 7.56-7.38 (m, 3H), 7.32-7.06 (m, 6H), 6.96-6.77 (m, 2H), 4.90-4.76 (bs, 1H), 4.04-3.82 (m, 3H), 3.40-3.15 (m, 5H+H_2O), 3.07-2.94 (m, 1H), 2.64-2.36 (m, 2H+DMSO), 2.23-1.68 (m, 14H). ES-LCMS *m/z* 732 (M+H).

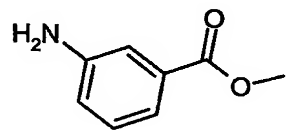
Example 1172

1,1,1-Trifluoro-*N*-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide



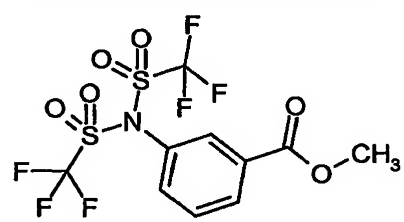


a) Preparation of methyl 3-amino-benzoate.



To a solution of 3-amino-benzoic acid (10.0 g, 72 mmol) in anhydrous methanol (100 ml) was added dropwise acetyl chloride (15 ml) with stirring under a nitrogen atmosphere. After stirring for 3 hours the volatiles were removed by spin evaporation in vacuo and the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate and then water. The organic layer was concentrated by spin evaporation in vacuo with the addition of dichloromethane (3 times) give methyl 5-amino-2-chlorobenzoate as a white solid. (9.8 g, 89%). ^{1}H-NMR (400 MHz, DMSO-d_6. δ 7.92-7.78 (m, 2H), 7.50-7.44 (m, 1H), 7.4-7.36 (m, 1H), 3.94 (s, 3H) ES-LCMS *m/z* 152 (M+H).

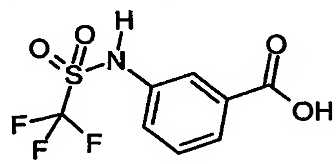
b) Preparation of methyl 3-{bis[(trifluoromethyl)sulfonyl]amino}benzoate.



Triflic anhydride (3.73 g, 13.2 mmol) was added dropwise to a solution of methyl 3-amino-benzoate (2.0 g, 13.2 mmol) and DIEA (2.3 ml) in dichloromethane (50 ml) at 0 °C while stirring under a nitrogen atmosphere. After warming to room temperature over 1 hour, the thick slurry was diluted with additional dichloromethane (200 ml) and washed with aqueous 1 N hydrochloric acid and the water. The dichloromethane layer was dried with

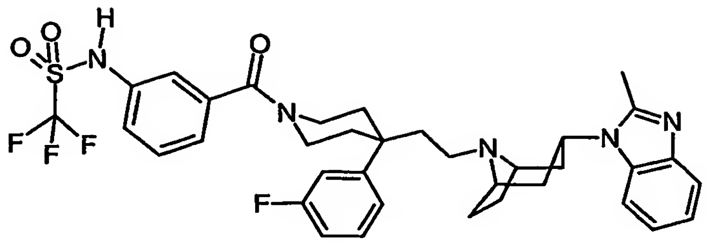
$MgSO_4$ and the volatiles were removed by spin evaporation in vacuo to give methyl 3-bis[(trifluoromethyl)sulfonyl]amino}benzoate as a tan oil (5.4 g, 100%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.73-7.65 (m, 2H), 7.55-7.50 (m, 1H), 7.44-7.36 (m, 1H), 3.95 (s, 3H). ES-LCMS *m/z* 416 (M+H).

c) Preparation of 3-{[(trifluoromethyl)sulfonyl]amino}benzoic acid.



A solution of methyl 3-{bis[(trifluoromethyl)sulfonyl]amino}benzoate (5.4 g, 13.0 mmol), sodium hydroxide (3.12 g, 78.0 mmol), methanol (125 ml) and water (125 ml) was stirred for 2 hours. The solution from concentration to 75 ml by spin evaporation in vacuo and dilution with 100 ml water was extracted with ethyl acetate. The aqueous layer was acidified with 12 N hydrochloric acid and again extracted with ethyl acetate. The organic layer was washed with water and concentrated by spin evaporation in vacuo, with the addition of dichloromethane (3 times) to give a residue that was dissolved in 1 N aqueous hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 times) and the organic layers were combined, washed with water, and concentrated by spin evaporation in vacuo to 3-{[(trifluoromethyl)sulfonyl]amino}benzoic acid as a solid (2.3 g, 66%). ^{1}H-NMR (400 MHz, DMSO-d_6):): δ 7.83-7.78 (m, 2H), 7.55-7.50 (m, 1H), 7.50-7.46 (m, 1H). ES-LCMS *m/z* 269 (M+H).

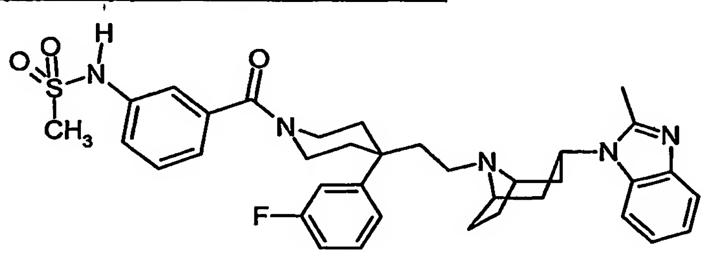
d) Preparation of 1,1,1-trifluoro-N-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

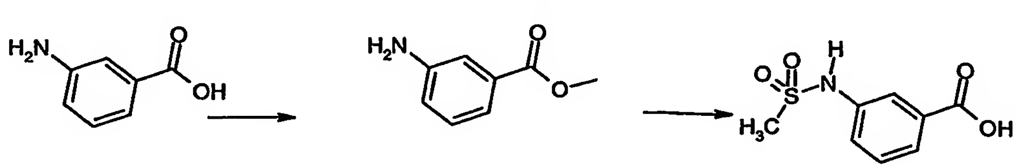


1,1,1-Trifluoro-*N*-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (72 mg, 100%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 3-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (73 mg. 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.83-8.68 (bs, 1H), 7.58-7.49 (m, 1H), 7.59-7.49 (m, 2H),7.49-7.38 (m, 2H), 7.21-7.05 (m, 4H), 7.02-6.91 (m, 2H), 6.79-6.67 (m, 1H), 5.03-4.76 (m, 1H), 4.13-3.96 (m, 3H), 3.57-3.01 (m, 6H), 2.54-2.39 (M, 5H), 2.24-1.97 (m, 8H), 1.97-1.68 (m, 3H), 1.31-1.14 (m, 2H). ES-LCMS *m/z* 698 (M+H).

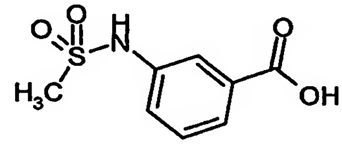
<u>Example 1173</u>

<u>*N*-{3-[(4-(3-Fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide</u>



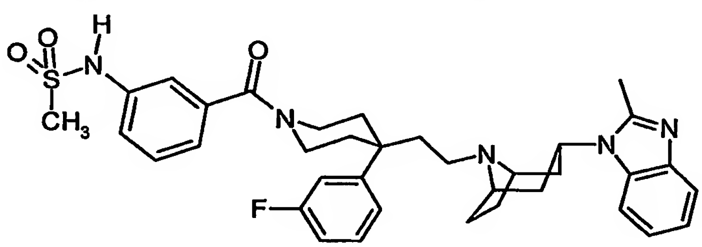


a) Preparation of 3-[(methylsulfonyl)amino]benzoic acid.



To a solution of methyl 3-amino-benzoate (2.0 g, 13.2 mmol) and pyridine (2.30 g, 29.1 mmol) in dichloromethane (50 ml) at –10 °C under a nitrogen atmosphere was slowly added methanesulfonyl chloride (2.25 ml, 29.1 mmol) by syringe. After 2 hours, water was added and the volatiles were removed by spin evaporation in vacuo. A solution of the residue and sodium hydroxide (3.175 g, 79.4 mmol) in methanol (50 ml) and water (50 ml) was stirred for 18 hours. The residue after removal of the volatiles by spin evaporation in vacuo was dissolved in 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and the volatiles were removed by spin evaporation in vacuo to give 3-[(methylsulfonyl)amino]benzoic acid as an oil. (1.32 g, 46 %). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.83-7.78 (m, 2H), 7.55-7.50 (m, 1H), 7.50-7.46 (m, 1H), 3.80 (s, 3H). ES-LCMS *m/z* 216 (M+H).

b) Preparation of N-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

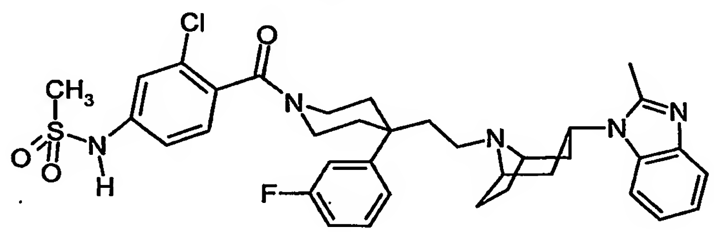


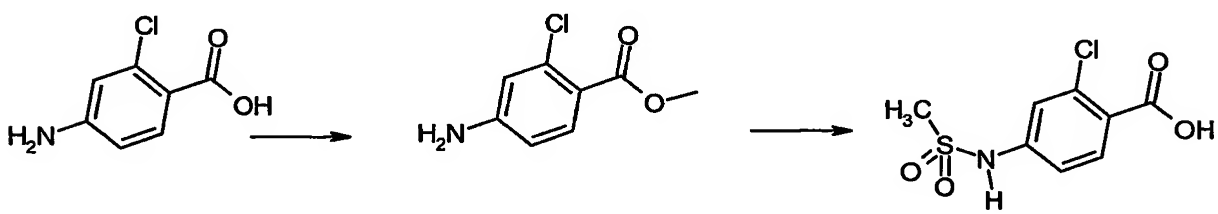
N-{3-[(4-(3-Fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (72 mg, 100%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol 3-

[(methylsulfonyl)amino]benzoic acid (73 mg. 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.90 (bs 1H), 7.49-7.49 (m, 1H), 7.44-7.31 (m, 3H), 7.27-7.20 (m, 3H), 7.19-7.15 (m, 1H), 7.14-7.00 (m, 4H), 4.55-4.39 (m, 1H), 3.91-3.79 (m, 1H), 3.53-3.40 (m, 1H), 3.40-3.09 (m, 2H), 3.03-2.96 (m, 3H), 2.51-2.45 (m, 5H), 2.44-2.40 (m, 3H), 2.40-2.30 (m, 2H), 2.17-1.96 (m, 2H), 1.91-1.70 (m, 4H), 1.64-1.52 (m, 2H), 1.25-1.10 (m, 1H). ES-LCMS *m/z* 644 (M+H).

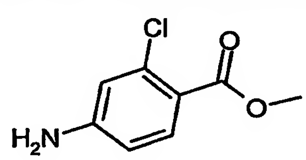
Example 1174

N-{3-Chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.





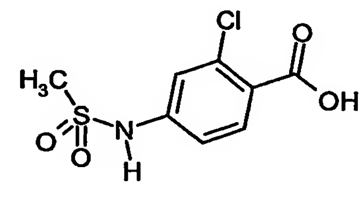
a) Preparation of methyl 4-amino-2-chlorobenzoate.



Methyl 4-amino-2-chlorobenzoate (5.1 g, 94 %) was obtained as solid from 4-amino-2-chlorobenzic acid (5.0 g, 29.1 mmol)) following the procedure outlined for ***methyl 5-amino-2-chlorobenzoate.*** ^{1}H-NMR (400 MHz, DMSO-

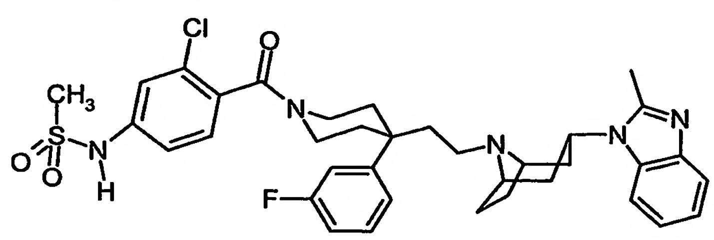
d$_6$): δ 7.64-7.57 (m, 1H), 6.65-6.57 (m, 1H), 6.51-6.39 (m, 1H), 6.16 (bs, 2H), 3.71 (s, 3H). ES-LCMS *m/z* 186 (M+H).

b) Preparation of 2-chloro-4-[(methylsulfonyl)amino]benzoic acid.



2-Chloro-4-[(methylsulfonyl)amino]benzoic acid (5.1 g, 94 %) was obtained as an oil from methyl 4-amino-2-chlorobenzoate (5.0 g, 29.1 mmol)) following the procedure outlined for ***3-[(methylsulfonyl)amino]benzoic acid.*** ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 13.11 (bs, 1H), 10.29 (bs, 1H), 7.83-7.80 (m, 1H), 7.24-7.22 (m, 1H), 7.21-7.18 (m, 1H), 3.11 (s, 3H). ES-LCMS *m/z* 250 (M+H).

c) Preparation of N-{3-chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

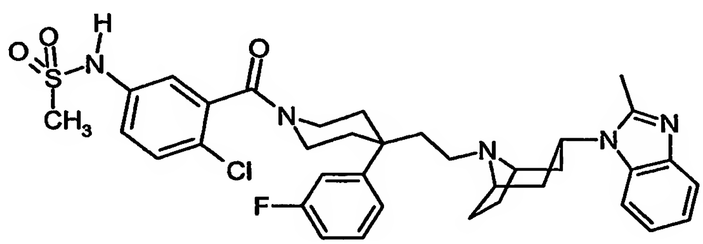


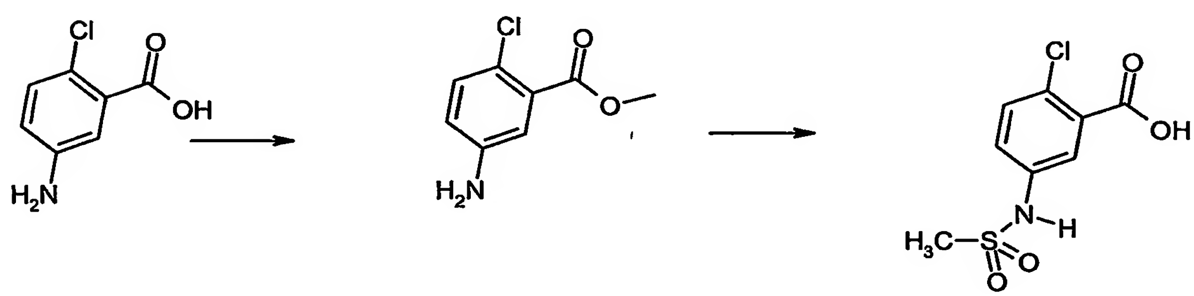
N-{3-Chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (29 mg, 17.4%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-chloro-4-[(methylsulfonyl)amino]benzoic acid (68 mg. 0.270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure

outlined in example 5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.55-7.44)m, 1H0,7.44-7.27 (m, 3H), 7.27-6.98 (m, 8H), 4.56-4.42 (m, 1H), 3.97-3.82 (m, 1H), 3.39-3.17 (m, 3H), 3.10-2.93 (m, 5H), 2.44-2.40 (m, 3H), 2.39-2.29 (m, 2H), 2.19-2.02 (m, 3H), 1.93-1.69 (m, 6H), 1.62-1.54 (m, 2H), 1.24-1.07 (m, 2H), 0.98-0.91 (m, 1H). ES-LCMS *m/z* 678 (M+H).

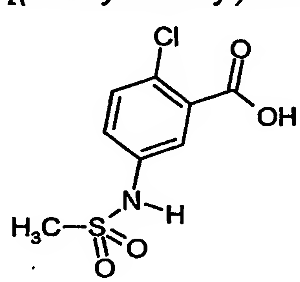
Example 1175

N-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide





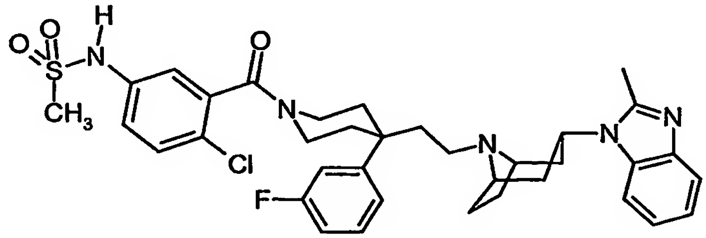
a) Preparation of 2-chloro-5-[(methylsulfonyl)amino]benzoic acid.



2-Chloro-5-[(methylsulfonyl)amino]benzoic acid (1.83 g, 68 %) was obtained as an oil from methyl 5-amino-2-chlorobenzoate (2.0 g, 10.8 mmol))

following the procedure outlined for ***2-chloro-4-[(methylsulfonyl)amino]benzoic acid***. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.46 (bs, 1H), 10.05 (s, 1H), 7.62-7.55 (m, 1H), 7.50-7.45 (m, 1H), 7.37-7.30 (m, 1H), 3.02 (s, 3H). ES-LCMS *m/z* 249 (M+H).

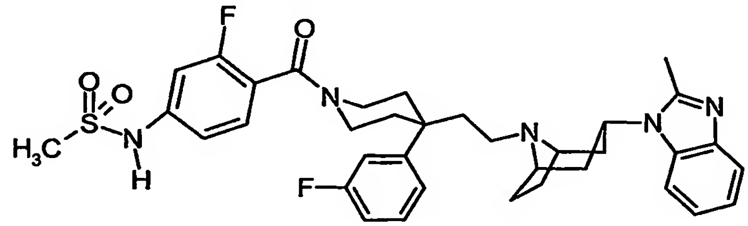
b) Preparation of N-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

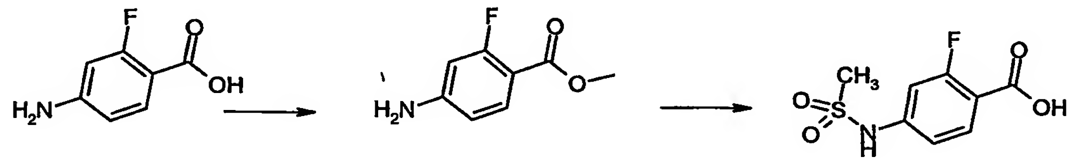


N-{4-Chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (103 mg, 61.6 %) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol 2-chloro-5-[(methylsulfonyl)amino]benzoic acid (68 mg. 0.270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.00 (bs, 1H), 7.57-7.47 (m, 2H), 7.45-7.34 (m, 2H), 7.28-7.21 (m, 3H),7.18-7.02 (m, 4H), 4.57-4.43 (m, 1H), 3.98-3.83 (m, 1H), 3.45-3.21 (m, 8H), 3.11-2.99 (m, 4H), 2.46-2.41 (m, 3H), 2.41-2.30 (m, 2H), 2.21-2.02 (m, 2H), 1.99-1.72 (m, 6H), 1.65-1.56 (m, 2H). ES-LCMS *m/z* 678 (M+H).

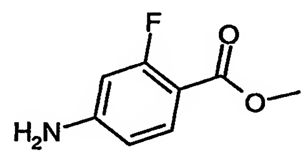
Example 1176

N-{3-Fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



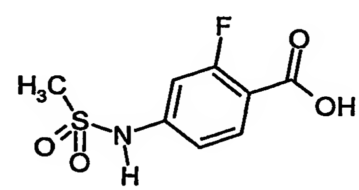


a) Preparation of methyl 4-amino-2-fluorobenzoate.



Methyl 4-amino-2-fluorobenzoate (1.98 g, 98 %) was obtained as solid from 4-amino-2-fluorobenzic acid (2.0 g, 12.90 mmol)) following the procedure outlined for ***methyl 5-amino-2-chlorobenzoate***. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.61-7.58 (m, 1H), 6.42-6.37 (m, 1H), 6.32-6.25 (m, 3H), 3.72 (s, 3H). ES-LCMS *m/z* 170 (M+H).

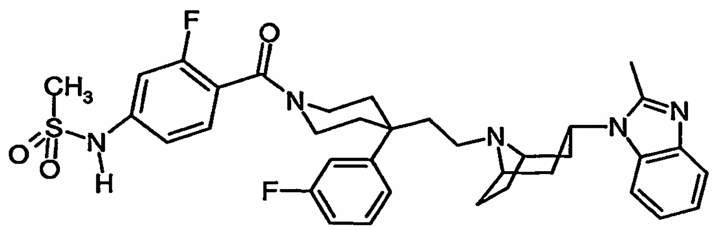
b) Preparation of 2-fluoro-4-[(methylsulfonyl)amino]benzoic acid.



2-Fluoro-4-[(methylsulfonyl)amino]benzoic acid (5.1 g, 94 %) was obtained as an oil from methyl 4-amino-2-fluorobenzoate (5.0 g, 29.1 mmol)) following the procedure outlined in example ***3-[(methylsulfonyl)amino]benzoic acid***. ^{1}H-NMR (400 MHz, DMSO-d_6): δ

7.69-7.59 (m, 1H), 6.45-6.40 (m, 1H), 6.40-6.32 (m, 3H), 3.72 (s, 3H). ES-LCMS *m/z* 234 (M+H).

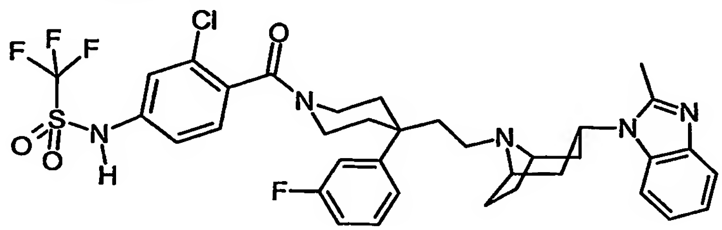
c) Preparation of N-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

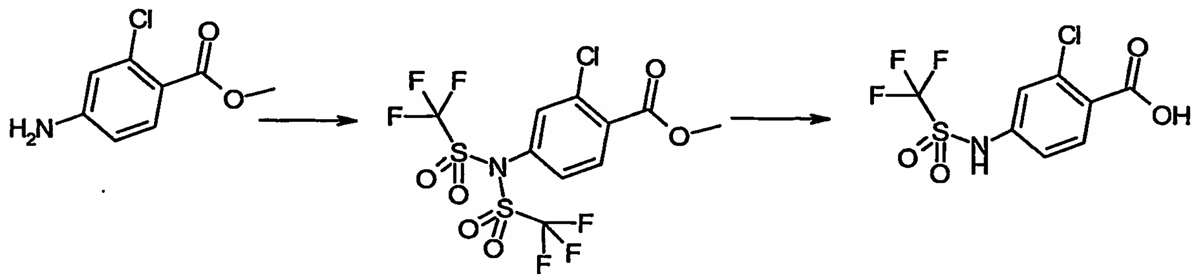


N-{3-Fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (26 mg, 15%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-chloro-4-[(methylsulfonyl)amino]benzoic acid (U20375/163/1) (68 mg. 0.270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.49-7.45 (m, 1H), 7.43-7.28 (m, 3H), 7.25-7.01 (m, 8H), 4.54-4.42 (m, 1H), 3.95-3.83 (m, 1H), 3.38-3.196 (m, 5H+H2O), 3.08-2.97 (m, 4H), 2.51-2.40 (m, 2H), 2.39-2.29 (m, 2H), 2.18-2.01 (m, 3H), 1.91-1.70 (m, 6H), 1.62-1.55 (m, 2H), 1.23-1.10 (m, 2H), 0.98-0.92 (m, 1H). ES-LCMS *m/z* 662 (M+H).

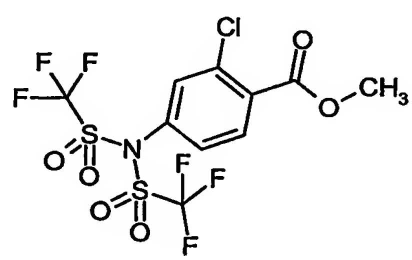
Example 1177

N-{3-Chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide





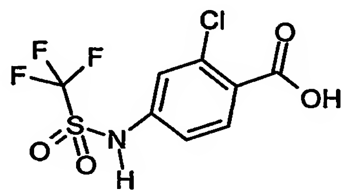
b) Preparation of methyl 4-{bis[(trifluoromethyl)sulfonyl]amino}-2-chlorobenzoate.



Triflic anhydride (3.73 g, 13.2 mmol) was added dropwise to a solution of methyl 4-amino-2-chlorobenzoate (2.45 g, 13.2 mmol) and ethyl[bis(1-methylethyl)]amine (2.3 ml) in dichloromethane (50 ml) at 0 °C while stirring under a nitrogen atmosphere. After warming to room temperature over 1 hour, the thick slurry was diluted with additional dichloromethane (200 ml) and washed with aqueous 1 N hydrochloric acid and the water. The dichloromethane layer was dried with $MgSO_4$ and the volatiles were removed by spin evaporation in vacuo to give methyl 4-

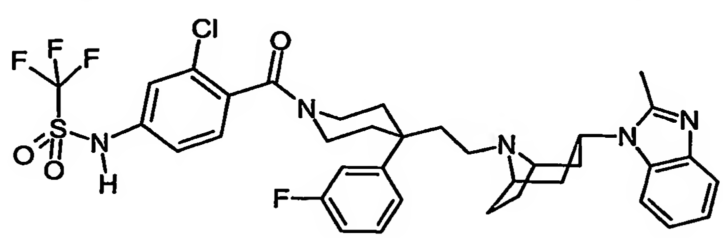
{bis[(trifluoromethyl)sulfonyl]amino}-2-chlorobenzoate as a tan oil (5.9 g, 100 %). ES-LCMS *m/z* 450 (M+H).

c) Preparation of 2-chloro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid.



A solution of methyl 4-{bis[(trifluoromethyl)sulfonyl]amino}-2-chlorobenzoate (5.9 g, 13.1 mmol), sodium hydroxide (3.12 g, 78.0 mmol), methanol (125 ml) and water (125 ml) was stirred for 2 hours. The solution from concentration to 75 ml by spin evaporation in vacuo and dilution with 100 ml water was extracted with ethyl acetate. The aqueous layer was acidified with 12 N hydrochloric acid and again extracted with ethyl acetate. The organic layer was washed with water and concentrated by spin evaporation in vacuo, with the addition of dichloromethane (3 times) to give a residue that was dissolved in 1 N aqueous hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 times) and the organic layers were combined, washed with water, and concentrated by spin evaporation in vacuo 2-chloro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid as a solid (3.6 g, 61%). ES-LCMS *m/z* 304 (M+H).

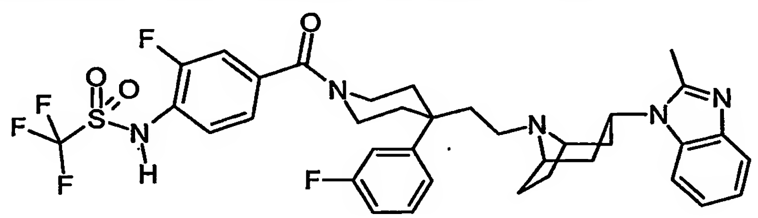
d) Preparation of N-{3-chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide.

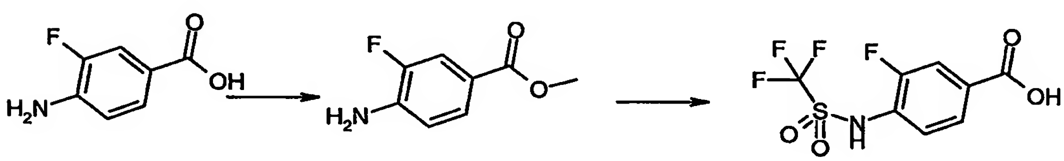


N-{3-chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (35 mg, 19%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-chloro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic (82 mg. 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 732 (M+H).

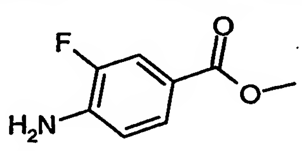
Example 1178

1,1,1-Trifluoro-*N*-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



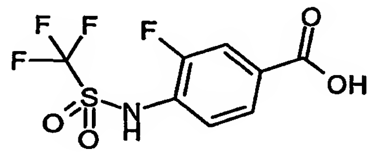


a) Preparation of Methyl 4-amino-3-fluorobenzoate.



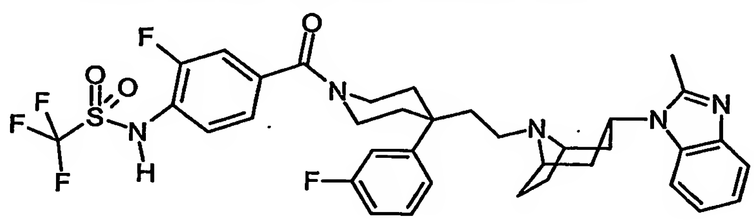
Methyl 4-amino-3-fluorobenzoate (1.01 g, 92 %) was obtained as solid from 4-amino-3-fluorobenzic acid (1.0 g, 6.4 mmol) following the procedure outlined in example 1171. ES-LCMS *m/z* 170 (M+H).

b) Preparation of 3-fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid.



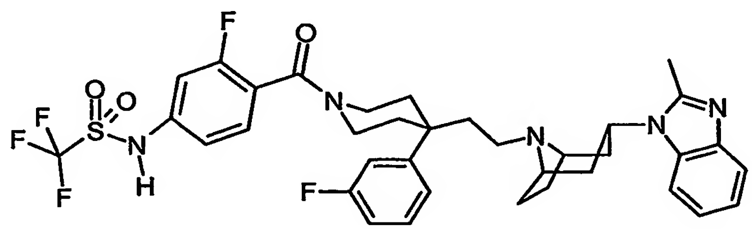
3-Fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (0.892 g, 97 %) was obtained as an oil from methyl 4-amino-3-fluorobenzoate (1.80 g, 6.39 mmol)) following the procedure outlined in example 1174. ES-LCMS *m/z* 288 (M+H).

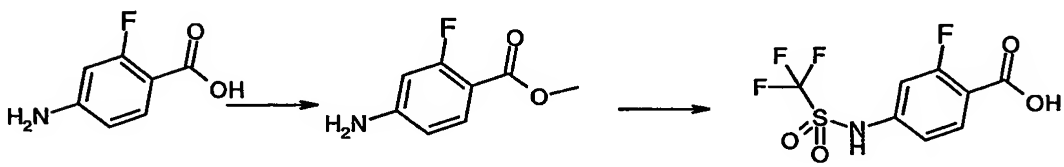
c) Preparation of 1,1,1-trifluoro-N-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



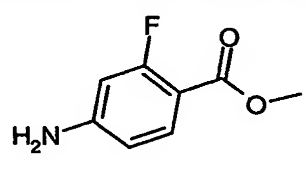
1,1,1-Trifluoro-*N*-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (85 mg, 48%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 3-fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (78 mg. 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 716 (M+H).

Example 1179
1,1,1-Trifluoro-*N*-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



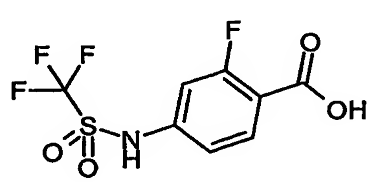


a) Preparation of methyl 4-amino-2-fluorobenzoate.



Methyl 4-amino-2-fluorobenzoate (1.85 g, 84 %) was obtained as solid from 4-amino-2-fluorobenzic acid (2.0 g, 12.90 mmol)) following the procedure outlined in example 1171. ES-LCMS *m/z* 170 (M+H).

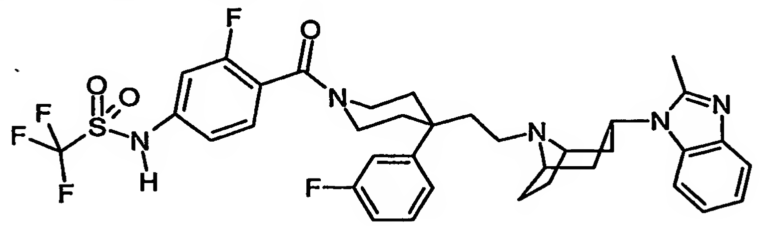
b) Preparation of 2-fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid.



2-Fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (1.32 g, 74 %) was obtained as an oil from methyl 4-amino-2-fluorobenzoate (1.05 g, 6.2

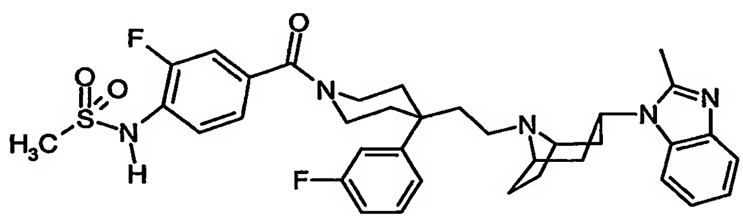
mmol)) following the procedure outlined in example 1174. ES-LCMS *m/z* 288 (M+H).

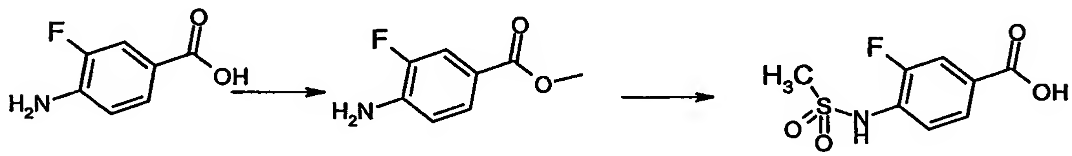
c) Preparation of 1,1,1-trifluoro-N-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



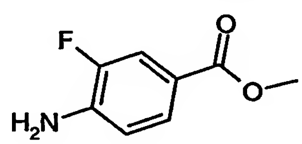
1,1,1-Trifluoro-*N*-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (85 mg, 48%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (78 mg. 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 716 (M+H).

Example 1180
N-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



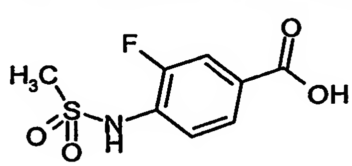


a) Preparation of methyl 4-amino-3-fluorobenzoate



Methyl 4-amino-3-fluorobenzoate (0.98 g, 90.0 %) was obtained as solid from 4-amino-3-fluorobenzic acid (1.0 g, 6.45 mmol)) following the procedure outlined in example 1171. ES-LCMS *m/z* 170 (M+H).

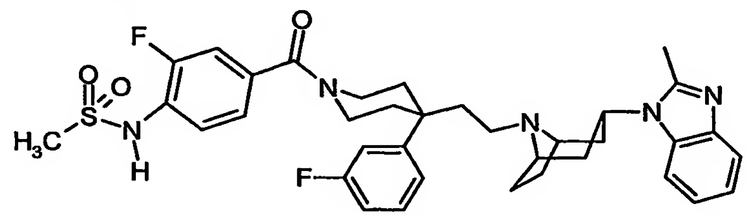
b) Preparation of 3-fluoro-4-[(methylsulfonyl)amino]benzoic acid.



3-Fluoro-4-[(methylsulfonyl)amino]benzoic acid (490 mg, 66 %) was obtained as an oil from methyl 4-amino-3-fluorobenzoate (0.54 g, 3.19 mmol)

) following the procedure outlined in example 1174. ES-LCMS *m/z* 234 (M+H).

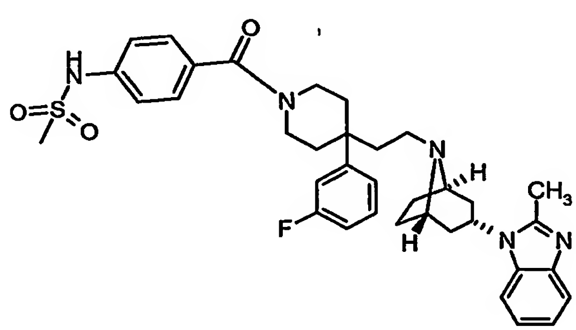
c) Preparation of N- {2-fluoro-4- [(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



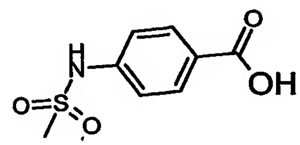
N-{2-Fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (92 mg, 52 %) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 3-fluoro-4-[(methylsulfonyl)amino]benzoic acid (U20375/147/1) (78 mg. 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 662 (M+H).

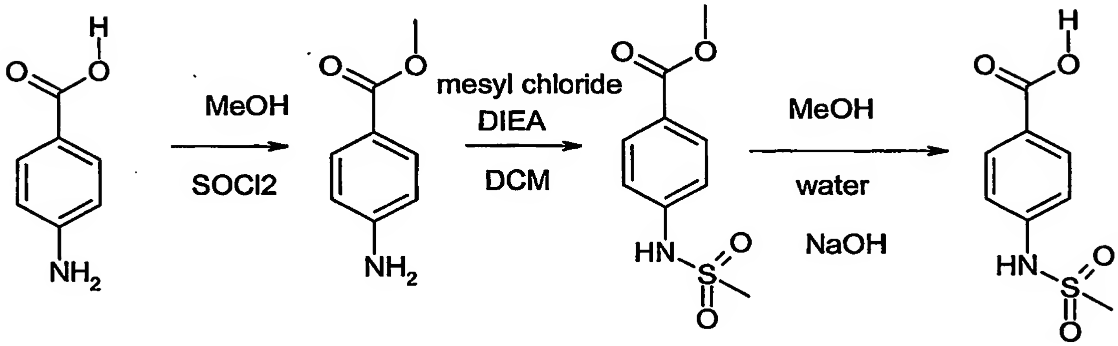
Example 1181

N-{4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide



The synthesis of 4-[(methylsulfonyl)amino]benzoic acid





2.1 g (15.6 mmol) of 4-aminobenzoic acid was dissolved in anhydrous MeOH, added 14.47g (123.3 mmol) of thionyl chloride dropwise under N2 while stirring at rt. After dtiring for four hours, solvents were removed and redissolved in 100 mL EtOAc and 40 mL of saturated NaHCO3 aq, stirred 30 min, separated and washed with 3 x 20 mL water. Organics were dried yielding 2.17g (yield 92.1%) of methyl 4-aminobenzoate. 1H NMR (300 MHz, CDCl3): 7.88 (2H, d, *J*=8.6 Hz), 6.66 (2H, d, *J*=8.6 Hz), 4.19 (2H, broad s), 3.88 (3H, s). 13C NMR (300 MHz, CDCl3): 167.8 (C=O), 151.4 (Cq), 131.9 (2x CH), 120.0 (Cq), 113.8 (2x CH), 50.9 (CH3).

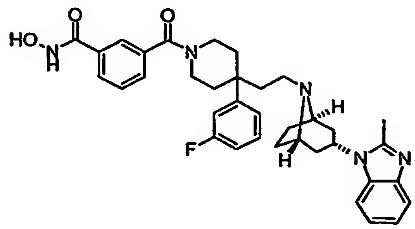
1.13g (7.48 mmol) of methyl 4-aminobenzoate was dissolved in 20 mL of anhydrous DCM and 1.97g (17.19 mmol) of mesyl chloride was added at 4 deg C, followed by the 2.22 g (17.19 mmol) of the diethylisopropylamine. Reaction was carried out overnight at room temperature resulting methyl 4-[(methylsulfonyl)amino]benzoate, which was used in the next step without additional purification.

3.6 g (90 mmol) of NaOH was added to the solution of methyl 4-[(methylsulfonyl)amino]benzoate in 40 mL methanol and 20 mL water and stirred overnight at room temperature. Solvents were then removed and the product purified by ethyl acetate extraction from 1N aqueous hydrochloric acid, providing 1.2g (yield 74.6%) of the 4-[(methylsulfonyl)amino]benzoic acid. 1H NMR in d-chloroform: 8.03 (2H, d, J=8.7 Hz), 7.34 (2H, d, J=8.7 Hz), 3.09 (3H, s). 13C NMR in d-chloroform: 131.2, 117.9, 38.6.

The synthesis of N-{4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide

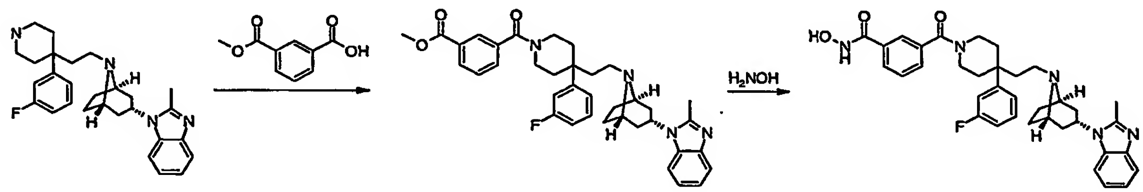
270 mg (0.61 mmol) of 1-((1R,5S)-8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride salt trihydrate was dissolved in the dichloromethane, and added 195 mg (0.91 mmol) of the 4-[(methylsulfonyl)amino]benzoic acid, 440 mg (0.91 mmol) of HATU and 391 mg (3.03 mmol) of the diethylisopropylamine an the reaction carried out as described in example 5, resulting in title N-{4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide, yield 32% after HPLC purification.
1H NMR (d4-methanol, 400 MHz): 7.53 (1H, m), 7.40 (4H, m), 7.31 (2H, d, J=7.7 Hz), 7.22 (4H), 6.99 (1H, m), 4.74 (1H, m), 4.09 (1H, broad s), 3.68 (1H, broad s), 3.39 (4H, m), 3.03 (4H, m), 2.52 (s, 3H), 2.45 (2H, m), 2.32 (1H, broad s), 2.23 (1H, broad s), 1.95 (10H, m), 1.71 (1H, m)

Example 1074



3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-*N*-hydroxybenzamide

Example 1074 was prepared according to scheme below.



1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (500mg, 0.962mmol) was combined with 3-[(methyloxy)carbonyl]benzoic acid (173mg, 0.962mmol) and DIPEA (373mg, 2.88mmol) in 8mL DMF and treated with HATU (366mg, 0.962mmol) at ambient temperature for 16h. The reaction mixture was treated with satd. $NaHCO_3$ which yielded a solid precipitate that was filtered off, washed with water and dried to give methyl 3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzoate (395mg, 0.649mmol, 67%) as a white solid. ES-LCMS *m/z* 609.1 (M+H).

Hydroxylamine.HCl (26mg, 0.360mmol) dissolved in 5mL EtOH was cooled in an ice bath and treated with 0.5M $NaOCH_3$ (1.92mL, 0.96mmol) for 15min with stirring. Methyl 3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzoate (183mg, 0.300mmol) was added to the reaction

mixture and allowed to stir 16h at ambient temperature. The reaction mixture was concentrated to dryness and purified by RP-HPLC on a C-18 column eluted with 0→50%CH_3CN in H_2O with 0.1% formic acid buffer. The appropriate fractions were combined and concentrated to give 3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-*N*-hydroxybenzamide (20mg, 0.032mmol, 9%) as a clear glass. ES-LCMS *m/z* 610.14 (M+H), 608.21 (M-1).

CC-Chemokine Receptor-5 Binding by Scintillation Proximity Assay

The compounds of this invention were evaluated as antagonists of CCR5 by high-throughput screening using scintillation proximity assay (SPA) binding that measures inhibition of binding of ^{125}I-MIP1□ to the human CCR5 chemokine receptor.

Human CCR5 receptors were expressed in Chinese Hamster Ovary (CHO) cells. Cells were grown in suspension and 50 to 80 ml CCR5 cell pellets were prepared.

Membranes were prepared according to the following procedure: 1) weighed pellet; 2) prepared an ice-cold 50 mM HEPES buffer, containing 0.0025 mg/ml Pefabloc, 0.0001 mg/ml Pepstatin A, 0.0001 mg/ml Leupeptin, 0.0001 mg/ml Aprotinin (protease inhibitor cocktail), pH 7.4; 3) homogenized pellet in 5 volumes of HEPES buffer; 4) homogenized again with a glass homogenizer for 10 to 20 strokes; 5) centrifuged homogenate at 18,000 rpm in a F28/36 rotor using a Sorvall RC26 PIUS refrigerated Centrifuge for 30 minutes; 6) discarded supernatant and resuspended pellet in 3 volumes of HEPES buffer; 7) homogenized and centrifuged again using steps 4-6 for two more times; 8) re-weighed pellet and homogenize in three times weight-to-volume of HEPES buffer; 9) placed aliquot 0.5 to 1.5 ml of the membrane preparation into small vials and stored at –80°C; 10) determined the protein concentration of the membrane preparation using the Bio-Rad or BCA

method; and 11) characterized the membrane homogenate for the assay conditions including protein concentration, optimal protein-to-bead ratio in SPA, and saturation curve to determine K_d and B_{max} (number of binding sites) in SPA.

The saturation curve binding experiment was performed by adding varying amounts of [^{125}I]MIP1α (0-8.5 nM) to membranes and beads in concentrations chosen from the optimal protein/bead ratio. The data was analyzed using a non-linear curve-fitting program. The K_d and B_{max} were derived from the curve.

Bacitracin 50 mg/ml was dissolved in deionized water, brought to a boil for 5 minutes (to destroy protease activity) and cooled. One milliliter aliquots were prepared and stored at –80°C.

Protease inhibitor cocktail was prepared by dissolving 25 mg/ml of Pefabloc, 1 mg/ml of Leupeptin, 1 mg/ml of Aprotinin and 1 mg/ml of Pepstatin A in 100% DMSO. The cocktail could be aliquoted and stored frozen at –20 °C until needed.

Any reagent bottles and reservoirs that come in contact with the radioligand were treated with Sigmacote to reduce sticking. Containers were rinsed with undiluted Sigmacote and with deionized water for several times and allowed to air dry before using.

Color quench assay was performed with a [^{125}I] SPA PVT color quench kit (Cat. No. RPAQ 4030, Amersham Ltd.). A color quench curve was generated for each Packard TopCount and was stored in each counting protocol specific for the assay. This was done to prevent colored compounds from quenching the scintillation counts.

Compounds of this invention were prepared for SPA according to the following protocol. Compounds for a single concentration determination (one shots) were delivered in 96 well Packard Optiplates containing 1 μl of compound in 100% DMSO in columns A1-H10 (80 compounds/plate). Column A11 to H11 was used for total binding (Bo: zero standard - bound radioactive counts in the absence of added inhibitor or test compound) (vehicle-5 μl of the appropriate DMSO concentration) and column A12 to D12

was used for determination of nonspecific binding (NSB). No further preparation was required. Compounds for concentration-response curves (10 points) were delivered in 96- Packard Optiplates containing 1 μl of compound in 100% DMSO in columns A1-H10. A 10-point concentration-response curve was desired for each compound with a starting high concentration of 30 μM (in the assauy final). Column A11 to H11 was used for total binding (Bo) (vehicle-5 μl of the appropriate DMSO concentration) and column A12 to D12 was used for determination of nonspecific binding. No further preparation was required.

Assay buffer was prepared by mixing 50 mM HEPES buffer (pH 7.4), 1 mM $CaCl_2$, 5 mM $MgCl_2$ which could be made ahead as a 100X stock, 1% BSA (bovine serum albumin), 0.5 mg/ml Bacitracin, and protease inhibitor cocktail (100 uL/100 ml). DMSO was added to equal a final concentration of 2% per well (includes compound %DMSO) if needed.

[^{125}I]MIP1α radioligand dilutions was prepared in containers treated with Sigmacote. Each 50 μCi vial was reconstituted with 0.5 ml of deionized water and stored at 4°C. The specific activity was 2,000 Ci/mmol. 50 μL (~60,000 cpm; 0.17 nM) of [^{125}I]MIP1α was added to each assay well.

Zero standard (Bo) was prepared by making a 20% DMSO solution and adding 5 μl of 20% DMSO solution to each well in columns A11-H11. This gave a final 2% DMSO concentration for the well when added to the 1% in the assay buffer.

A stock dilution of MIP1α at 100uM was made using deionized water and aliquoted and frozen. The MIP-1α stock solution was diluted to a concentration of 2 μM in the same 20% DMSO solution used above. 5 μl of the resultant solution was added to the wells in column A12 to D12 to give a final assay concentration of 100 nM. This procedure was conducted in a Sigmacote-treated container.

The final assay concentration for the membrane was 15 μg per well. SPA beads were prepared by adding 5 ml of assay buffer to a 500 mg vial. The final concentration of SPA beads in the assay was 0.25 mg/well.

Membranes and beads were premixed as a 1:1 (membrane:bead) mixture and maintained at mixture at 4°C with constant stirring. 50 μl of the mixture was added to each assay well. After all reagents had been added to the plates (total assay volume 100 μl), plates were shaken for 4 hours at room temperature. After 4 hours, the plates were placed on the TopCount in a count the plates on the TopCount for 30 sec per well using an appropriate program (i.e., one with a quench curve established for the conditions of the assay).

Data reduction was performed using the Microsoft Excel Addins Robofit or Robosage. For single concentration assays (one shots), the result of each test well was expressed as % inhibition using the following formula: 100*(1-(U1-C2)/(C1-C2)), where U1 was the unknown sample in cpm observed in a particular well, C1 was the average of column 12 cpm observed in the absence of any added inhibitor, and C2 was the average of column 11 cpm observed in the presence of 1uM of MIP1α. For concentration-response assays, the result of each test well was expressed as %B/Bo (% total specific binding) using the following formula: 100* (U1-C2)/C1-C2). Curves were generated by plotting the %B/Bo versus the concentration and the IC_{50} was derived using the equation y=Vmax*(1-(x^n/(k^n+x^n))).

For controls and standards, each plate contained 12 wells of total binding (column A11-H11). The cpm/well were averaged and used in data reduction as value C1. Each plate also contained 4 wells of non-specific binding (wells A12-D12). The counts of these wells were averaged and used in data reduction as value C2. A standards plate was included in each experiment. This plate contained a 14-point concentration-response curve (in triplicate) for the standard compound MIP1α at a starting concentration of 1 μM. The average historical pK_i obtained with MIP1α was 7.6.

The relevant biological response field for a single concentration (one shots) was % inhibition. Inhibition values of >40 or >50% were considered positive responses. The relevant biological response field for a concentration-response experiment was pK_i.

HOS Assay (Also referred to as HOS-LTR-Luciferase Assay)

HOS-CD4.CCR5-LTR-Luciferase (Bioresource Registration # 21164): Human Osteosarcoma cell line was engineered to overexpress human CD4 and human CCR5 (AIDS Repository cat# 3318) stabily transfected with HIV-1-LTR-Luciferase reporter.

Growth and Maintenance of the HOS-CD4.CCR5-LTR-Luciferase cell line: The cells were propagated in DMEM containing 2% FBS. Cells were split by standard trypsinization when confluency reached 80% (roughly every 2 to 3 days).

Titering of virus stocks: HIV-1 virus stocks were titered in the assay system in order to obtain an estimate of the number of infectious particles per unit volume (described as RLU/ml). Virus stocks were diluted into DMEM containing 2% FBS and assayed as described in the "procedure" section below.

Procedure: Black-walled 96-well tissue culture plates were seeded with HOS-CD4.CCR5-LTR-Luciferase @ 0.6 to 1.2×10^3 cells per well in 50µl DMEM containing 2% FBS and placed in a humidified incubator @ 37^0C, 5% CO_2 overnight. The following day, test compounds were titrated 4-fold at 2X the final concentration in DMEM + 2% FBS + 0.2% DMSO. 50□l of titrated compound was transferred to the HOS cells and the plates were placed in a humidified incubator at 37°C, 5% CO_2 for 1 hr. An additional 60□l of 2X titrated compound was transferred to a clear-walled 96-well tissue culture plate and 60□l of HIV (diluted to appropriate m.o.i.) was added to each well and thoroughly mixed. 100□l of the HIV/compound mixture was transferred to the black-walled plates containing 100□l of cells/compound. The plates were placed in a humidified incubator at 37°C, 5% CO_2 for 72hr. Following the 72 hour incubation, 150□l of supernatant was removed and 50□l of reconstituted LUCLITE (kit reagent) was added to each well. Each plate was sealed and read in a Topcount (Packard) luminometer at 1s/well.

Data Reduction: Relative Light Units (RLU) were expressed as % control (RLU at drug concentration / RLU no drug)*100 = % Control. IC_{50}

values were determined by any one of the following four nonlinear regression models:

y=Vmax*(1-(x^n/(K^n+x^n)))+Y2;

y=Vmax*(1-(x^n/(K^n+x^n)));

y=Vmax*(1-(x/(K+x)))+Y2;

y=Vmax*(1-(x/(K+x)));

where K is IC_{50}, Y2 is baseline, and N is Hill Coefficient.

Each of the compounds of the present invention provides a pIC_{50} value of at least 5 when tested in each of the above-described assays.

Test compounds are employed in free or salt form.

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments which utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of the invention is to be defined by the appended claims rather than by the specific embodiments which have been represented by way of example.